VOLUME 79 • JANUARY 1959 • NUMBER 1

ARCHIVES OF DERMATOLOGY

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Murray C. Zimmerman

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Frederick J. Szymanski

Acquired Vascular Tumors of the Skin in the Adult
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Granuloma Faciale
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Fred Levit

Piedra
J. M. Hitch

Vibrapuncture Treatment for Creeping Eruption
John van de Erve

Control of Small Vessel Bleeding After Dermabrasive Surgery
Murry M. Robinson

Prednisolone in Aerosol Form
Frederick Reiss and Andrew Kallos

Prednisolone (Meti-Derm) as an Aerosol for Dermatoses
Harry M. Robinson Sr.

Obituary: Emerson James Trow, M.D.

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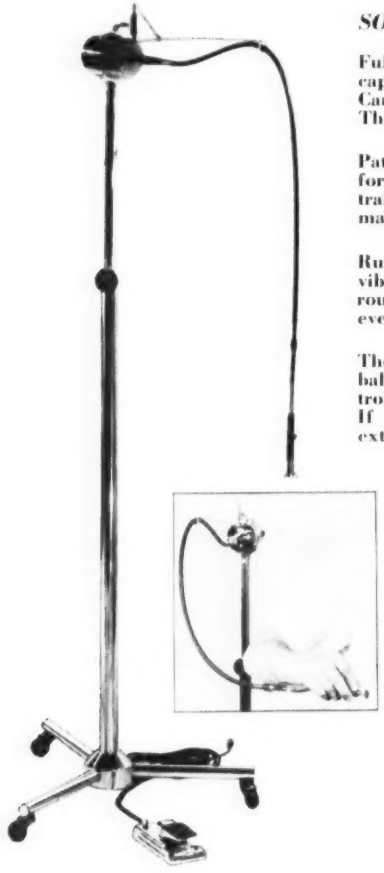

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TABLE OF CONTENTS

VOLUME 79 JANUARY 1959 NUMBER 1

ORIGINAL ARTICLES

PAGE

Chronic Penicillin Urticaria from Dairy Products, Proved by Penicillinase Cures
Murray C. Zimmerman, M.D., Whittier, Calif. 1

Pityriasis Lichenoides et Varioliformis Acuta
Frederick J. Szymanski, M.D., Chicago 7

Acquired Vascular Tumors of the Skin in the Adult
Louis H. Winer, M.D., and Gerald H. Levin, M.D., Los Angeles 17

Smooth-Muscle Tumors of the Skin
Hamilton Montgomery, M.D., and R. K. Winkelmann, M.D., Ph.D., Rochester, Minn. ... 32

Granuloma Faciale
Capt. Waine C. Johnson (MC); Col. Robert S. Higdon (MC), U. S. Army, and Elson B. Helwig, M.D., Washington, D. C. 42

Fungistasis of Hydrocortisone and Certain of Its Analogues
Robert L. Sawyan, M.A., and Richard L. Sutton Jr., M.D., Kansas City, Mo. 53

Genetic Studies on Acanthosis Nigricans
Helen Ollendorf Curth, M.D., and Bertha M. Aschner, M.D., New York 55

The Basal-Cell Nevus
J. B. Howell, M.D., Dallas, Texas, and Marcus R. Caro, M.D., Chicago 67

Pathology of the Dermatitis Produced by the Urticating Caterpillar, Automeris Io
David L. Jones, M.D., and Joseph H. Miller, Ph.D., New Orleans 81

Influence of Specific Antibody on Herpes Simplex Infections in Tissue Culture
Clayton E. Wheeler, M.D., and Charles M. Canby, M.S., Charlottesville, Va. 86

Fluorescent Material in Scales, Nails, and Hair
Fred Levit, M.D., Chicago 96

CLINICAL NOTES, NEW INSTRUMENTS AND TECHNIQUES

Piedra
J. M. Hitch, M.D., Raleigh, N. C. 99

Vibrapuncture Treatment for Creeping Eruption
John van de Erve, M.D., Charleston, S. C. 101

Control of Small Vessel Bleeding After Dermabrasive Surgery
Murry M. Robinson, M.D., Washington, D. C. 101

Prednisolone in Aerosol Form
Frederick Reiss, M.D., and Andrew Kallos, M.D., New York 103

Prednisolone (Meti-Derm) as an Aerosol for Dermatoses
Harry M. Robinson Sr., M.D., Baltimore 103

OBITUARIES

Emerson James Trow, M.D. 106

SOCIETY TRANSACTIONS

Bronx Dermatological Society 108
Chicago Dermatological Society 112
Los Angeles Dermatological Society 115
Joint Meeting of the Los Angeles Dermatological Society and the Metropolitan Dermatological Society of Los Angeles 116
The Metropolitan Dermatological Society of Los Angeles 121
Philadelphia Dermatological Society 123
THE NEW, NEWER, AND NEWEST 127

REGULAR DEPARTMENTS

Abstracts from Current Literature 128
Announcement: Man Sought by F. B. I. 134
Announcements 136
Books 138

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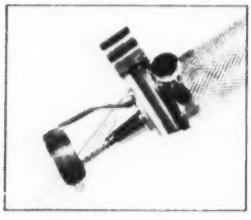

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1. Eisenberg, B. C.: Clinical Medicine *5*:897-904 (July) 1958.
2. Feinberg, A. R., et al.: J. Allergy *29*:358 (July) 1958.
3. Robinson, H. M., et al.: So. Med. J. *50*:1282 (Oct.) 1957.

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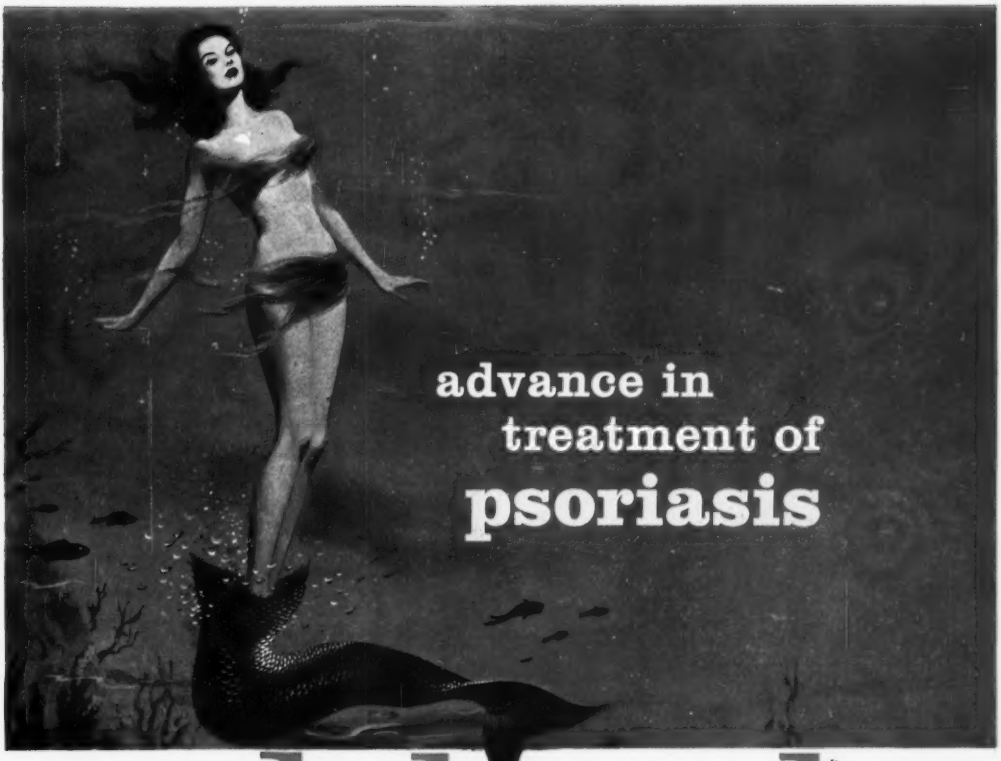

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2. *Shelley, W. B.; Harun, J. S., and Pillsbury, D. M.:* J.A.M.A. *167:959, 1958.*
3. *Rein, C. R.; Fleischmajer, R., and Rosenthal, A. L.:* J.A.M.A. *165:1821, 1957.*
4. *Appel, B.; Tye, M. J., and Leibsohn, E.: To be published.*
5. *Friedlaender, S., and Friedlaender, A. S.:* Antib. Med. & Clin. Therap. *5:315, 1958.*

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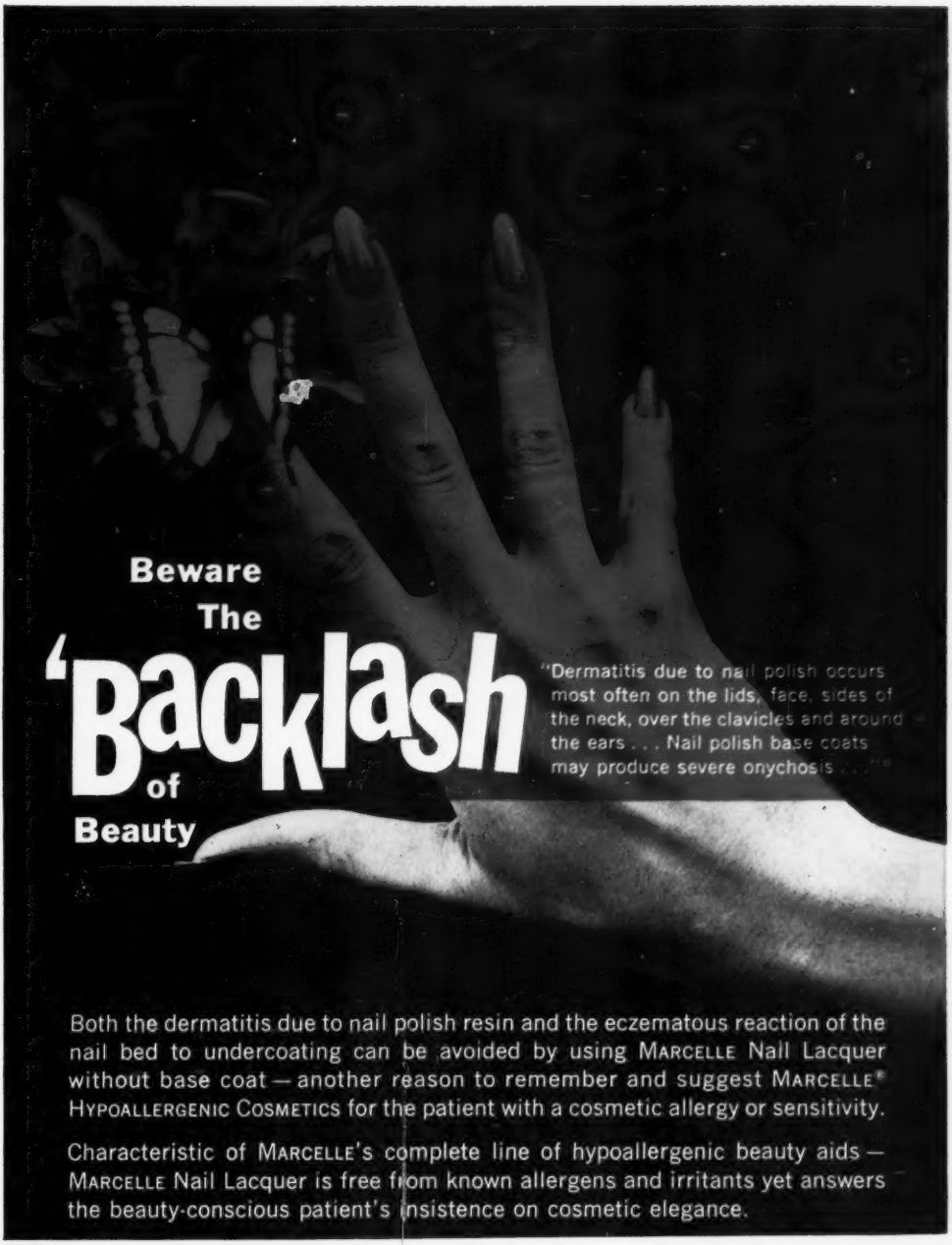
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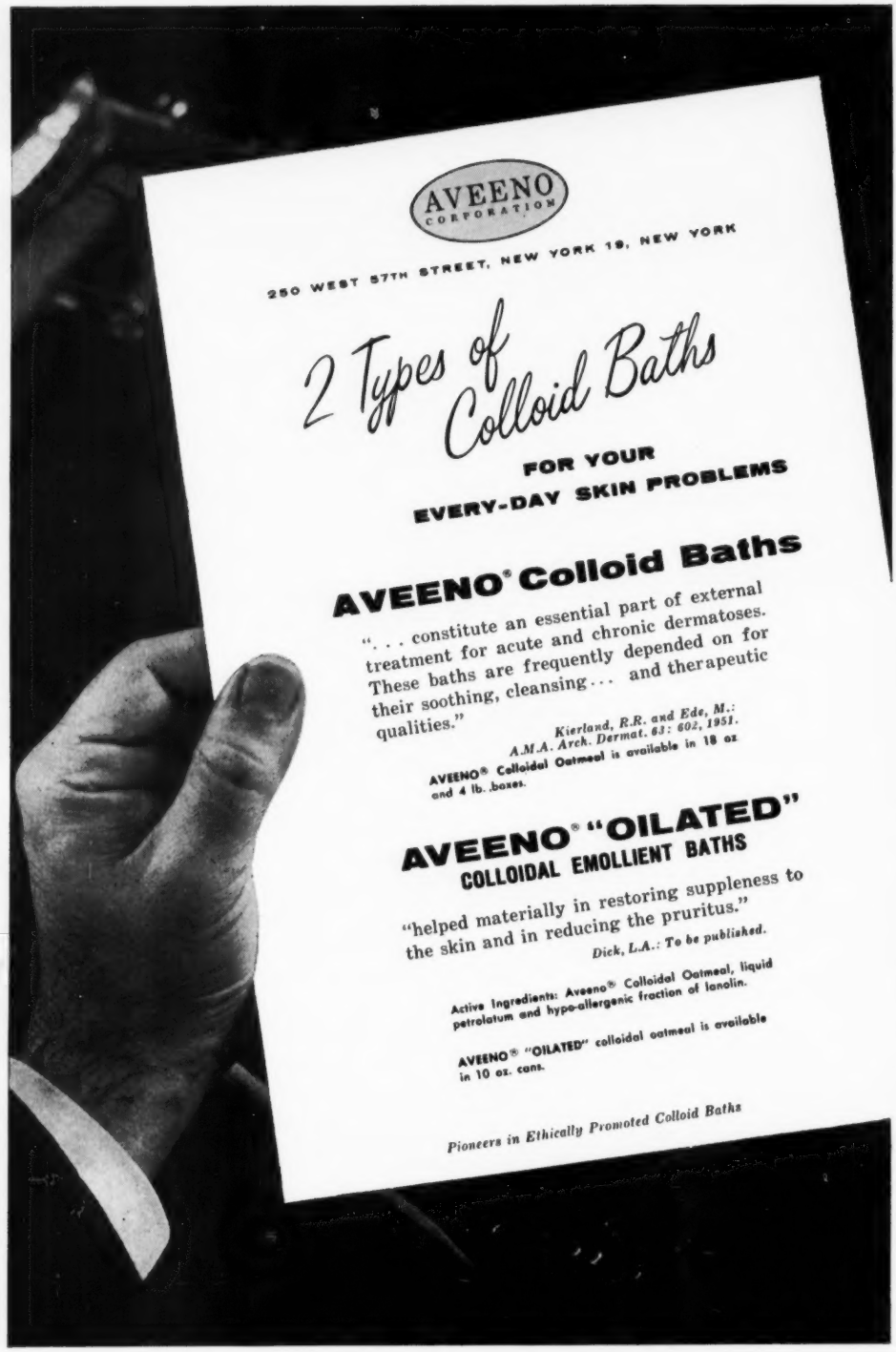
*Andrews, G. C.: Diseases of the Skin, ed. 4, Philadelphia, Saunders, 1954, pp. 117, 118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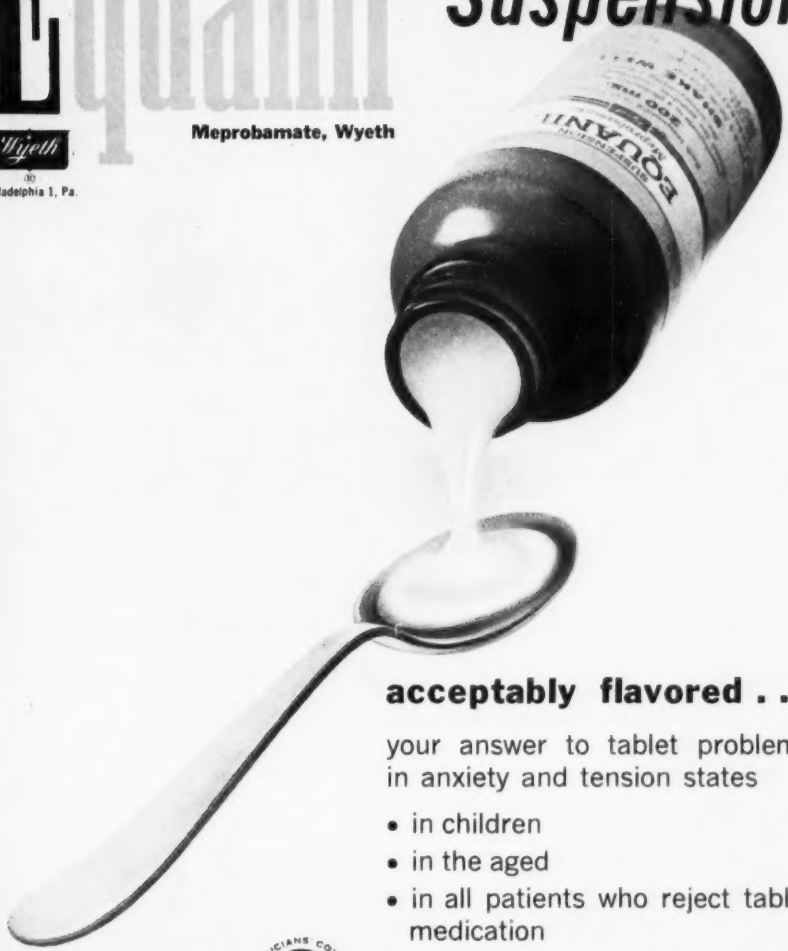

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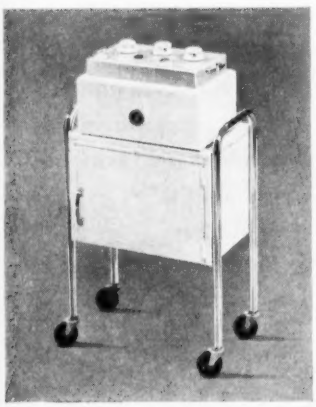

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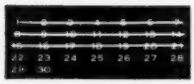

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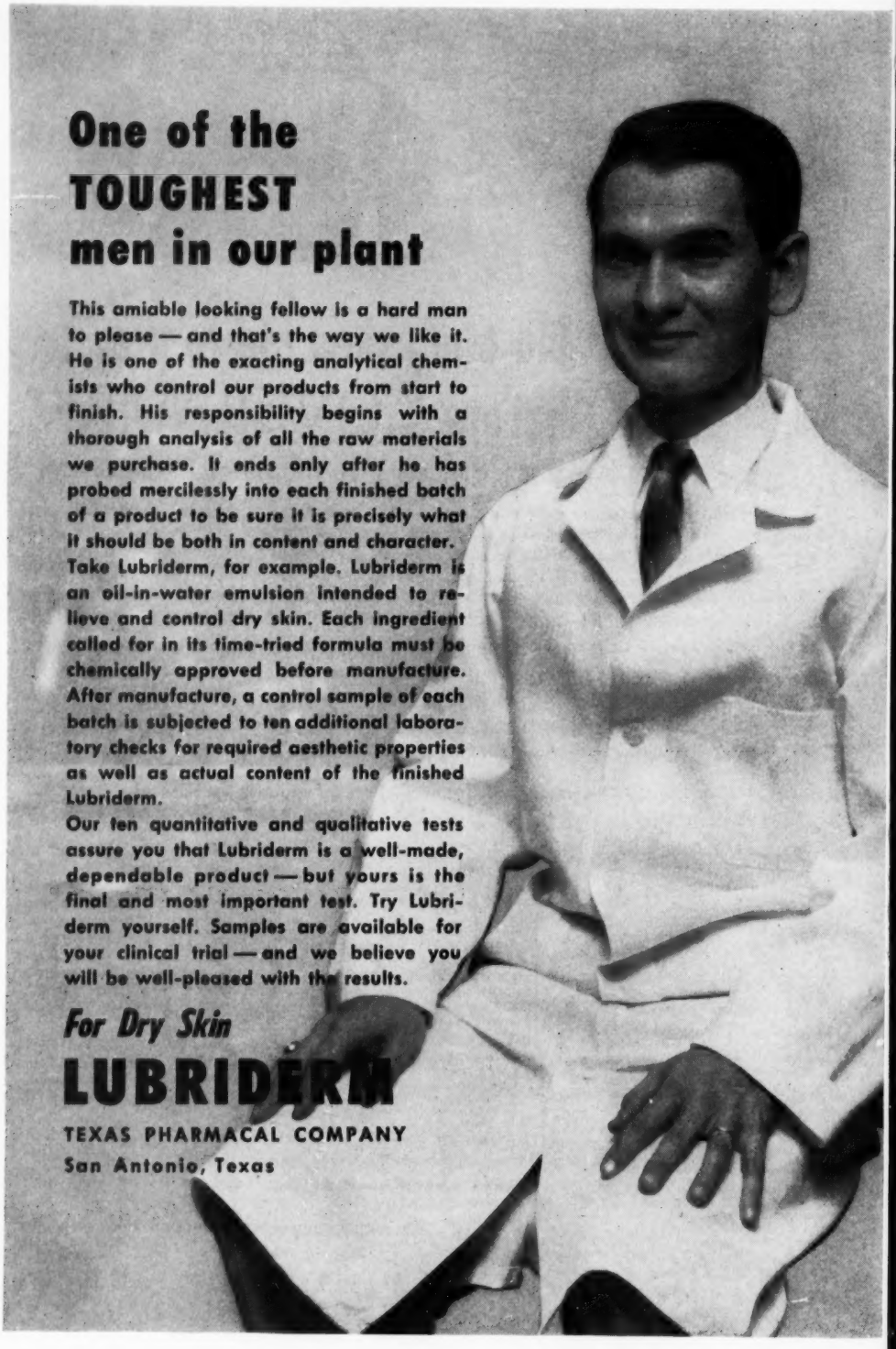

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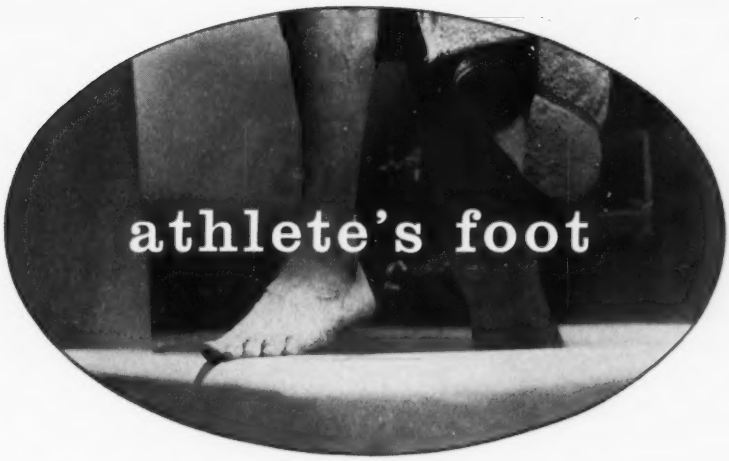

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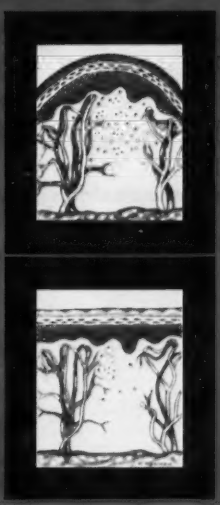

1. Welsh, A. L., and Ede, M.: J.A.M.A. 159:158, 1955.

Additional Clinical Publications on Tarcortin:

Clyman, S. G.: Postgrad. Med. 21:309, 1957 • Steiberg, J.: J. M. Soc. New Jersey 53:37, 1956 • Abrams, B. P., and Snow, C.: Clin. Med. 3:839, 1956 • Steiberg, J.: Am. Practitioner 8:1404, 1957

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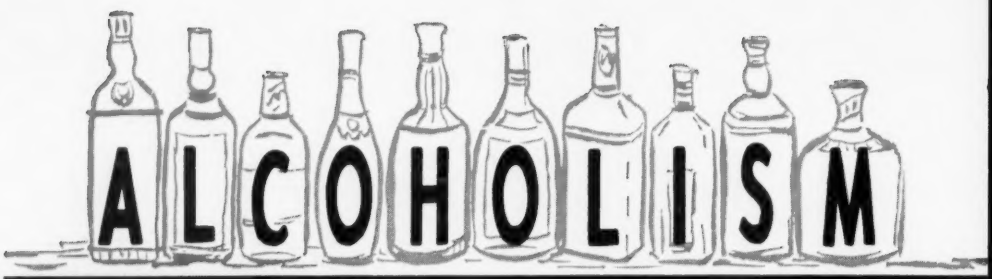

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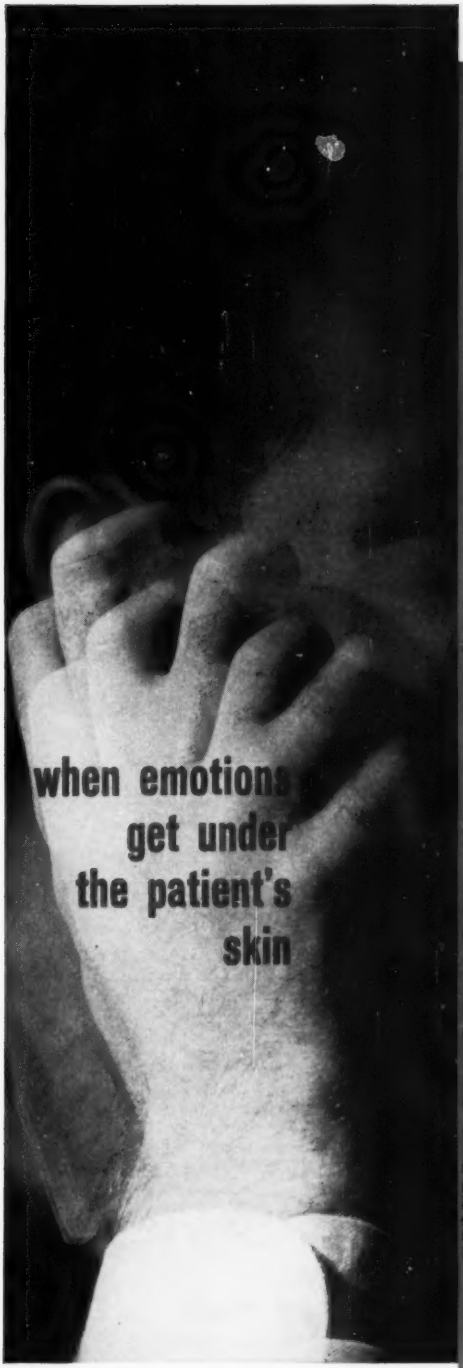

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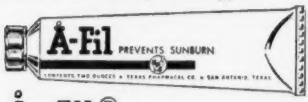

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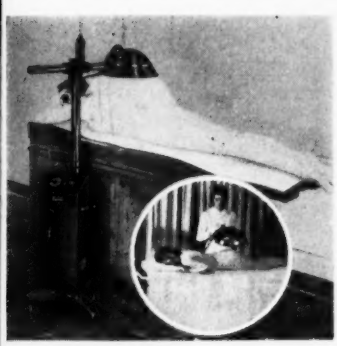

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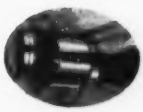

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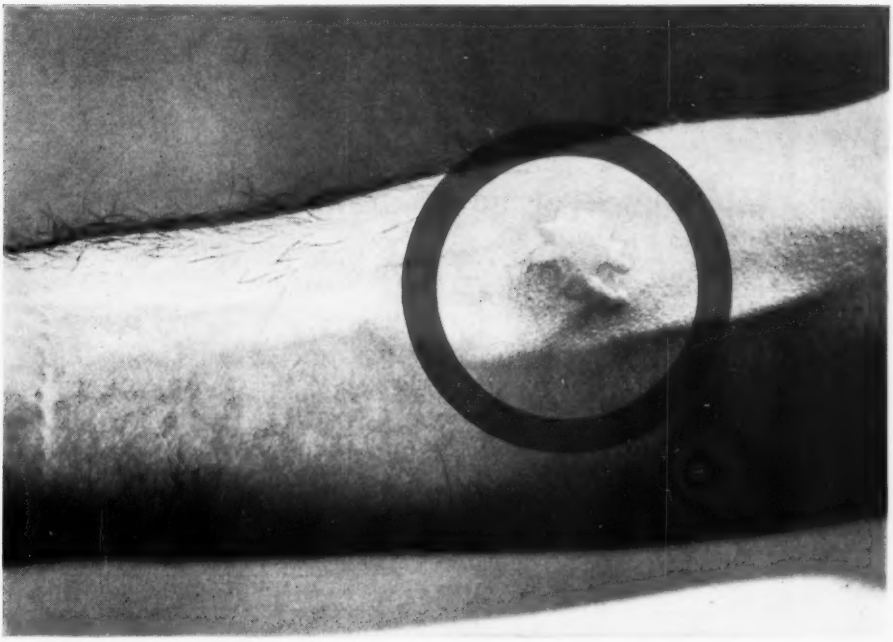

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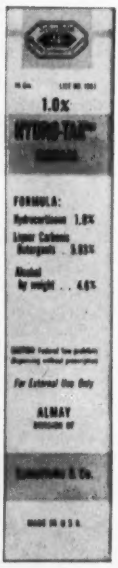

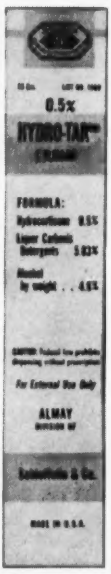

A.M.A. ARCHIVES OF
DERMATOLOGY

Chronic Penicillin Urticaria from Dairy Products. Proved by Penicillinase Cures

MURRAY C. ZIMMERMAN, M.D., Whittier, Calif.

Introduction

Penicillin reactions have produced over 1,000 deaths in the U. S. A.[1] The reactions are increasing steadily in both frequency and severity. Part of this increase may be due to allergies developed by the daily exposure of millions of Americans to penicillin-contaminated dairy products.[2,3] This article is written to review the subject and to present four case reports *proving* for the first time that penicillin contaminating milk causes allergic reactions.

Penicillin is widely used to treat mastitis in cows.[4,5] From this use, it contaminates a high percentage of American milk.[2,3,6] Penicillin in milk may sensitize nonallergic people or may provoke or prolong reactions in previously sensitized patients. Dr. Henry Welch, the Director of the Division of Antibiotics of the Food and Drug Administration (FDA), summarizing the problem in 1957, stated, "We do not have a single *proved* case of a reaction following the ingestion of fluid milk known to contain penicillin."[3] This statement was correct at that time, because diagnostic proof through therapeutic response to penicillinase was not then possible. As proof of the allergenicity of dietary traces of penicillin, the following evidence is now offered on four patients:

1. Each patient had a previous typical allergic reaction to penicillin.

2. The previous symptoms of known penicillin reaction were duplicated repeatedly by ingestion of dairy products.

3. The reactions cleared rapidly after an injection of penicillinase—a penicillin-destroying enzyme with no effect on anything but penicillin.[7]

4. The patients could eat dairy products without subsequent allergic reaction if given a prophylactic injection of penicillinase first.

Review

Mastitis in Cattle.—At any given time, more than 25% (6,500,000) of the 26,000,000 dairy cattle in the United States have mastitis.[8] This affects one or more of the four quadrants of the cow's udder. It may be caused by many strains of bacteria, most commonly by Staphylococcus pyogenes var. aureus and Streptococcus agalactiae.[4,5]

Milk from cows with mastitis smells and tastes bad. Mastitis cuts milk production of a cow 50% in quality and 25% in butterfat content,[8] hence its elimination is profitable.

Penicillin Treatment of Mastitis.—Therapy in 1946 was 20,000 units of soluble penicillin, by catheter instillation up the teat duct into the affected quadrant. As penicillin became cheaper, and as resistant strains of organisms began to develop, *insoluble* penicillin was used, and the recommended dosage became progressively higher. Since 1950, standard therapy has been 1,000,000 units instilled "at any suspicion

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From the University of Southern California School of Medicine Department of Medicine (Dermatology); Maximilian E. Obermayer, Chairman and Head of Department.

of mastitis." At least 49% of this instilled penicillin can be recovered from the milk. Other antibiotics have been used as substitutes or in conjunction, but penicillin has remained the treatment of choice.

Penicillin in Milk.—In 1948, and subsequently, there were complaints from the dairy industry that milk was so heavily contaminated with penicillin that it could not be turned into cheese.[9-13] Investigation showed that 0.1 units of penicillin per milliliter of milk partially inhibited, and 1.0 units completely inhibited cheese-making strains of bacteria. The complaints of cheese-makers have been numerous and vociferous, since this represented an economic loss.

Presence of penicillin is explained by inadequate discard of milk from udders treated for mastitis. It is also suggested by many authors, always by apophasis, that penicillin is used by unscrupulous dairymen to lower the bacterial count of substandard milk. (The grading of milk, "A," "B," and "C," is not on quality, but purely on bacterial count.)

Many articles have appeared in the nonmedical literature reporting penicillin levels of routine commercial milk samples. Measurable quantities of penicillin were found in as high as 96% of milk samples tested. Statements such as "We have all drunk milk contaminated with penicillin" [6] abound. A 1957 report of investigation by the FDA, after spot-checking 1,700 grocery store samples from 48 states and the District of Columbia, stated that 11% were contaminated with measurable amounts of penicillin, the maximum being 550 units per quart of milk.[3]

Previous Efforts at Control of Penicillin Contamination in Milk.—The FDA, as well as many state control agencies, recommended labeling penicillin sold for treatment of mastitis with the suggestion that milk from a treated quadrant be discarded for three days. ("Most" soluble penicillin is eliminated from milk after three days of milking; insoluble penicillin persists for eight days. It has been stated repeatedly that even the suggested three-day discard is ignored.)

The FDA has recommended that milk containing antibiotics be considered as "adulterated." Legislation to this effect has been introduced in some states. In 1957, the FDA restricted the previous 1,000,000 unit packets of penicillin used in treating mastitis to a future maximum of 100,000 units. They have also been searching, so far without success, for a long-lasting harmless dye to add to each penicillin packet which would discolor the milk for three days, forcing its discard.[3]

Previous Efforts to Prove Allergenicity. On Sept. 10, 1956, a medical advisory panel met with the Commissioner of the FDA to consider public-health aspects of the presence of antibiotics in market milk. Two panel members were selected to study highly sensitive human volunteers to determine whether ingestion of milk containing concentrations of penicillin found in market milk would cause allergic manifestations. The recent availability of Neutrapen* (penicillinase purified for parenteral use) has obviated the necessity for this dangerous, inconclusive, and unsatisfactory approach.

Evidence of Allergenicity.—Contamination of a high percentage of milk with bactericidal quantities of penicillin has been shown.[2,3,6,9-13] A 2 qt. milk drinker could ingest over 1,000 units daily. The fact that the penicillin "naturally" present in milk has not previously been proved to cause allergic reactions is outweighed by the fact that *this is almost a billion times more penicillin than has previously been shown necessary to provoke reactions.* Coleman and Siegel reported a patient with a reaction on passive transfer to 0.00001 units of penicillin.[14] Bierlein's patient went into shock

*Penicillinase, as used in all reported cases of human patients, was Neutrapen, purified from the secretion of Bacillus cereus Strain NRRL B-569 by SchenLabs Pharmaceuticals, Inc., and provided for research purposes by B. Marr Lanman, M. D., Director of Clinical Research, SchenLabs Pharmaceuticals, Inc.

when skin tested with 0.000003 units of penicillin.[15]

Injection is not necessary. Carter and Cope's patient went into anaphylactic shock and coma within seconds after applying penicillin ointment to her eyelid margins.[16] Comparing these almost molecular quantities to the quantities of penicillin ingested in milk, further proof should not be necessary, unless penicillin is bonded or inactivated by its mixture with milk. That it is not is shown by case histories below.

Penicillinase—Summary.—Penicillinase is an enzyme which destroys penicillin, rendering it nonantigenic and nonantibiotic. One 800,000 unit injection of Neutrapen injectable penicillinase in human volunteers maintains the blood free from measurable quantities of penicillin for four to seven days, even though 800,000 unit injections of penicillin are continued twice daily throughout this time.[7] This shows that *penicillinase is excreted slowly, its effect persisting from four to seven days after one injection.*

If any penicillin remains in the system (for example, from a prior injection of long-acting insoluble repository penicillin), or if new penicillin exposure occurs, a new outbreak of allergic symptoms may be expected [17,18] after the penicillinase effect has worn off. These subside with more penicillinase. Previous clinical reports on penicillinase in the treatment of penicillin reactions indicate that the response is predictable and the drug highly effective. It does not treat the allergic reaction per se; it destroys the antigen provoking the reaction. In over 90% of previously reported cases, one or two injections of penicillinase have cleared all symptoms in 12 to 96 hours.

Penicillinase Identity Test.—The FDA differentiates penicillin from other antibiotics by the "penicillinase identity test." A zone of inhibition develops on culture plates of Sarcina lutea (sensitive to 0.005 unit of penicillin per cubic centimeter) when exposed to samples of suspected substance (e. g., milk). No zone of inhibition develops around another portion of the same substance previously incubated with penicillinase. This is "positive identification of penicillin." [19]

The in vitro procedure uses an observable characteristic (inhibition of growth) of a living organism (S. lutea) as a biologic end-point indicator. In this form, the test is sensitive to 0.005 unit of penicillin per cubic centimeter. The test should not be less valid because a living patient rather than a test tube is used as a "container" for the reaction. The "in vivo" biologic end-point indicator (freedom from allergic symptoms) achieved as an easily observable characteristic of another living organism (Homo sapiens) is a far more sensitive indicator. Bierlein's [15] patient, for example, would be a biologic indicator for 0.000000-000003 unit of penicillin per cubic centimeter of patient, if as much as two-thirds of the test injection of penicillin was thoroughly mixed in the patient. For this reason, the rapid response to penicillinase of the patients reported in this article is considered strong evidence.

Report of Cases

Case 1.—This 26-year-old man had urticaria and arthralgia for three weeks after a penicillin injection in 1953. In 1957, his doctor prescribed oral penicillin "O" and assured him that he could not be allergic to this because it was oral and because it was Type "O." Ten days later, the patient developed hiving, joint swelling, and bullous erythema multiforme. He was treated with cortisone, corticotropin (ACTH), ephedrine, antihistamines, and calcium, all in heroic dosage, for the next six weeks. He was bedridden and miserable in spite of therapy. Physical examination six weeks after onset revealed a widespread, severe erythema multiforme, scattered palm-sized flaccid bullae, and a swollen reddened right knee joint, acutely painful on motion.

All other therapy was discontinued. The patient was given 800,000 units of Neutrapen intramuscularly (two months after his last penicillin). Subsequent to this, no new lesions developed and old areas cleared in 48 hours.

Six days after penicillinase, the patient developed mild hiving in friction areas; 800,000 units of Neutrapen again gave complete rapid clearing. *He was told at this time not to eat dairy products, ice cream, Roquefort or bleu cheese, etc.*

For seven weeks subsequently, the patient had intermittent, transient, and self-limited attacks of mild hiving. He then flared enough to return for further treatment. He was under psychic stress, grieving over separation from his wife, who had left him during the time that he was disabled, and was also under physical stress, trying to "make up for lost time" by going to school an additional six hours a day after working an eight-hour shift. These were considered possible causes for urticaria, *since the patient denied penicillin exposure.* However, 800,000 units of Neutrapen cleared him in a few hours.

Several weeks later, the patient's mother telephoned me on her own initiative, to inform me that her son was the equivalent of an ice cream and milk shake drunkard. She said that he would avoid eating dairy products for days, but eventually would go on an ice cream and milk shake "binge." Each of these "orgies" had been followed by a new outbreak of hiving. She said he had been ashamed to mention this to me. (Since he was suing his family doctor for prescribing penicillin, I felt this might also be a factor.) She also stated that he had consumed dairy products with impunity during the week following each of his Neutrapen injections and that after the third injection he had tried unsuccessfully to provoke a flare by massive dairy product ingestion. A telephone conversation with the patient, pointing out to him the importance of avoiding further contacts with dairy products, resulted in complete permanent clearing of his urticaria. Discussion of this factor with his attorney also resulted in dropping the malpractice suit against his family doctor.

CASE 2.—This patient had a repository penicillin injection seven days before he developed severe urticaria, erythema multiforme, arthritis, arthralgia, and fever. For 60 days, his symptoms were partially suppressed by massive doses of corticotropin, prednisolone, antihistamines, epinephrine, calcium, etc. His maintenance dose of prednisolone had then been cut to 15 mg. daily, with constant moderate hiving on this dosage.

Nine weeks after penicillin, he was given 800,000 units of Neutrapen and cleared 95% in 48 hours. Prednisolone was discontinued without flare. Seven days after penicillinase, he had a mild outbreak of urticaria only; 800,000 units of Neutrapen cleared this in a few hours. Since then, the patient has had mild repeated attacks but only after ingestion of dairy products. Each flare has been urticarial and has cleared completely with Neutrapen. Four outbreaks have been produced at the request of his internist or me. As little as 8 oz. of milk will bring on a new attack.

This patient has had a total of 11 injections of Neutrapen. He remains symptom-free on a milk-free diet. If he takes Neutrapen in advance, he can eat dairy products with impunity for four to eight days, depending on the dosage of Neutrapen and the quantity of dairy products consumed in the later days. A saline injection (which the patient thought was Neutrapen), followed by ingestion of dairy products, resulted in routine urticaria.

CASE 3.—This patient had twice had persistent urticarias after penicillin injections, always after eating Roquefort cheese and usually after any quantity of milk or ice cream.

The day after an injection of 1 cc. of poliomyelitis vaccine (a brand with 10-20 units of penicillin per cubic centimeter) he developed an urticarial reaction, which continued in spite of corticotropin, antihistamine, and corticosteroid therapy. On the 18th day, he received 800,000 units of Neutrapen. All other therapy was discontinued; in 24 hours, the patient was symptom-free. On my urging, he ate Roquefort cheese for the next two days without recurrence.

This patient stated that he voluntarily limited his intake of dairy products because he had found from experience that they gave him hives. He refused to be a party to any further experimentation with penicillinase prior to or subsequent to his ingestion of milk and/or cheese because the one penicillinase injection had given him a sore hip for 24 hours.

CASE 4.—This 35-year-old woman received her last penicillin injection Dec. 23, 1957, for an industrial injury. Progressive urticaria started Dec. 29. She had had no previous urticaria, penicillin allergy, or other allergy.

On Dec. 30 she had severe generalized urticaria and was given 800,000 units of Neutrapen. Clearing was dramatic, within 12 hours. She was completely clear on the fourth day, then flared on the sixth day (Jan. 5). *She was told not to eat dairy products and Roquefort cheese.* On Jan. 7, she received 800,000 units of Neutrapen, with rapid clearing. On Jan. 10, she had a few new hives, clearing *and remaining clear* after a third 800,000 units of Neutrapen, Jan. 11.

On Feb. 4, she was seen again with a new severe outbreak of urticaria. *She denied all penicillin exposure.* On my insistence that she must have had a new exposure if penicillin was the inciting allergen and my refusal to give her penicillinase, she finally admitted that she ate Roquefort cheese three hours before the hiving started. Afterward, she stated that she had eaten this before the last flare, too. She laughed and said, "I didn't think you could find out so easy if I cheated a little bit." (Her urticaria was an industrial disability, so her reluctance to admit outside factors is understandable.)

Penicillinase cleared her again, with no flare during the next three days, although she ate Roquefort at my request. On Feb. 13, she had

had no hiving. Between Feb. 13 and March 7 she produced five mild self-limited urticarial reactions subsequent to five ingestions of Roquefort cheese, at my request.

Penicillinase Diagnosis and Management of Urticaria

Chronic urticaria is notoriously difficult to cure. It is even more difficult to ascribe to a proven etiologic agent. Any patient with chronic urticaria, in whom penicillin sensitivity is suspected, should have 800,000 units of Neutrapen. Clearing in 12 to 96 hours, and staying clear for four to seven days, suggests that the inciting allergen is penicillin. Patients clearing after a penicillinase injection, who relapse after four to seven days (i. e., when all the injected penicillinase has been excreted or broken down), should abjure milk, ice cream, other dairy products, and Roquefort or bleu cheeses containing crude Penicillium species molds. Since percutaneous absorption of penicillin secreted by fungus parasites on the skin has been suggested as a sensitizing or eliciting factor in allergic response,[21] any existing dermatomycotic infection should be treated. Repeated small doses of penicillinase might be given to prevent urticaria or for the occasional patient who wants to "splurge" on an orgy of milk shakes, ice cream, or other dairy delicacies. Certified raw milk might also be tried, since it is claimed to be penicillin-free.

Comment

The foregoing case histories would indicate that penicillin in dairy products not only *can* act but *is* acting as an eliciting dose for allergic reactions. It is probably also acting to sensitize previously nonallergic patients.

A report by Epstein described patients with chronic penicillin reactions lasting up to 15 months.[20] When Neutrapen was made available on a research basis, and I was looking for penicillin allergies on which to try it, I called Dr. Epstein to see whether any of these patients might still be active and suitable for penicillinase treatment. He stated that his entire series of patients had recovered after he stopped their consumption of dairy products.

While the amounts of penicillin necessary to produce an allergic reaction have been shown to be molecular, and while penicillin eruptions in my experience have cleared without recurrence a few hours after one injection of Neutrapen, after continuing unabated for as long as 5 months, a 15-month allergic eruption, without new exposure to the antigen, is unlikely. Epstein's patients were probably reacting to the penicillin in dairy products.

It is obvious now, as it has been for many years, that the contamination of dairy products with penicillin and other antibiotics is undesirable. The FDA has taken many steps to control this. Increased publicity is necessary to explain to the dairy farmer the viewpoint of the allergist toward microgram doses of penicillin. A dye added to penicillin packets used for treating mastitis, as suggested by the FDA, would be an excellent measure. Until the present time, there has been no way to prove that penicillin was the allergen, in cases of milk allergy where there have been unofficial and unsubstantiated complaints by physicians to the FDA. The penicillinase in vivo identity test here described makes such identification easy. As may be noted in Cases 1 and 4, deliberate deception by patients for compensation or lawsuit purposes was uncovered by this test.

Summary

Traces of penicillin contaminating dairy products have previously been suspected but never *proved* as a cause of allergic reactions. Proof of allergenicity of penicillin in dairy products in four patients is based on the following evidence: (*a*) Patients had previous allergic reactions to penicillin. (*b*) This previously known penicillin allergic reaction was duplicated repeatedly after ingestion of dairy products. (*c*) The reaction cleared rapidly after injection of penicillinase—a penicillin-destroying enzyme with no effect on anything but penicillin.

(*d*) The patients could eat dairy products without subsequent allergic reaction if given a prophylactic injection of penicillinase first.

Even more stringent efforts should be made to eliminate penicillin contamination of American milk. (The 1957 estimate was that 11% of milk samples are contaminated with measurable amounts of penicillin.)

Patients with chronic urticaria where penicillin sensitivity is suspected should be given a test injection of penicillinase. If urticaria clears for four to seven days, penicillin sensitivity was probably the cause.

Patients with chronic urticaria, where penicillin sensitivity is proved or suspected, should have dairy products, ice cream, and Roquefort or bleu cheeses containing Penicillium species molds eliminated from their diets.

If patients have a flare-up four to seven days after a penicillinase injection, there is residual penicillin in the system which has not been destroyed. Penicillinase injections should be repeated at four- to seven-day intervals, as necessary, to stop symptoms.

If more than eight days pass before a new outbreak of allergic symptoms after an injection of penicillinase, then the penicillinase had destroyed all the penicillin in the system at that time. The new outbreak suggests that the patient either has had a new exposure to penicillin or that his new reaction is due to some other allergen.

301 E. Hadley St.

REFERENCES

1. Feinberg, S. M., and Feinberg, A. R.: Allergy to Penicillin, Editorial, J. A. M. A. 160:778-779 (March 3) 1956.

2. Zimmerman, M. C.: Penicillin Urticaria, Schoch Letter, Dallas, Texas, October, 1954, p. 56.

3. Welch, H. C.: Problems of Antibiotics in Food, as the Food and Drug Administration Sees Them, Am. J. Pub. Health 47:701 (June) 1957.

4. Little, R. B.: The Intramammary Therapy of Bovine Mastitis, J. Am. Vet. M. A. 108:127 (March) 1946.

5. Zweig, J.: Procaine Penicillin G in the Bovine Udder, Vet. Rec. 61:811 (Dec. 3) 1949.

6. Casselberry, N. H.: Role of Penicillin in Mastitis Control, N. Am. Vet. 33:768 (Dec.) 1946.

7. Becker, R. M.: Effect of Penicillinase on Circulating Penicillin, New England J. Med. 254: 952 (May 17) 1956.

8. Trump, F.: Aureomycin for Mastitis, Mich. Farmer 104:16 (Feb 4) 1950.

9. Hood, E. G., and Katznelson, H.: The Effect of Penicillin on the Acid Producing Ability of Starters, Canad. Dairy & Ice Cream J. 28:32, 1949.

10. Krienke, W. A.: Penicillin in Milk, a Hazard to Starters, Buttermilk and Cottage Cheese Manufacture, Milk Dealer 39:126, 1949.

11. Krienke, W. A.: Penicillin vs. Cheese, Hoard's Dairymen 95:180, 1950.

12. Beale, Clyde: Penicillin Affects Milk, Country Gent. 54:183 (Feb.) 1950.

13. Hanson, H. C.; Wiggins, G. E., and Boyd, J. C.: Modern Methods of Mastitis Treatment Cause Trouble in the Manufacture of Fermented Dairy Products, J. Milk Technol. 13:359, 1950.

14. Coleman, M., and Siegel, B.: Studies in Penicillin Hypersensitivity: II. The Significance of Penicillin as a Contaminant, J. Allergy 26:253, 1955.

15. Bierlein, K. J.: Repeated Anaphylactic Reactions in a Patient Highly Sensitized to Penicillin, Ann. Allergy 14:35, 1956.

16. Carter, E. S., Jr., and Cope, C. B.: Anaphylaxis Due to Topical Penicillin, J. Allergy 25:270 (May) 1954.

17. Zimmerman, M. C.: Penicillinase Treatment of 52 Patients with Allergic Reactions to Penicillin, Antibiotics Ann., pp. 312-320, 1957-1958.

18. Zimmerman, M. C.: The Prophylaxis and Treatment of Penicillin Reactions with Penicillinase, Clin. Med. 5:305 (March) 1958.

19. Welch, H. C., Ph. D., Director, Division of Antibiotics, Bureau of Biological and Physical Sciences, Food and Drug Administration, Washington 25, D. C.: Personal communication to the author.

20. Epstein, E.: Chronic Urticaria Following Penicillin Therapy, California Med. 74:429 (June) 1951.

21. Uri, J.; Szathmary, S., and Herpay, Z.: Production of an Antibiotic by Dermatophytes Living in Horn Products, Nature, London 179:1029 (May 18) 1957.

Pityriasis Lichenoides et Varioliformis Acuta

Histopathological Evidence That It Is an Entity Distinct from Parapsoriasis

FREDERICK J. SZYMANSKI, M.D., Chicago

The belief that pityriasis lichenoides et varioliformis acuta is a variant of parapsoriasis is based mostly on the assumption that there is a histopathological resemblance between the two conditions. Mucha emphasized the microscopic similarities of pityriasis lichenoides et varioliformis acuta and pityriasis lichenoides chronica. Since this original description, many observers, including Habermann, have agreed with Mucha's concept. Recent studies by me have disclosed distinctive microscopic alterations in pityriasis lichenoides et varioliformis acuta. These histopathological changes not only distinguish the two conditions but they indicate a pathogenesis not considered previously. The results of histopathological and histochemical examination in Mucha-Habermann's disease and all forms of parapsoriasis will be discussed. This report will not include a discourse on the morphologic features and clinical behavior of these two diseases.

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Department of Dermatology and Syphilology, University of Illinois College of Medicine (Service of Dr. Marcus R. Caro).

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Materials and Methods

The present investigation was conducted on biopsy tissues obtained from 62 separate patients. Of these, there were 18 cases of pityriasis lichenoides et varioliformis acuta, 37 cases of pityriasis lichenoides chronica, 5 patients with parapsoriasis en placques, and 2 with parakeratosis variegata. All tissues were fixed in formalin, and paraffin-block sections were stained with hematoxylin and eosin. Additional sections were stained by the following methods: Giemsa stain, Gomori's iron reaction, Gomori's reticulum stain, Gomori's aldehyde fuchsin stain for collagen and elastic tissue, and Bennhold's Congo red stain for amyloid. Sections from three cases of Mucha-Habermann's disease were compared histochemically with four cases of pityriasis lichenoides chronica by the following methods: Montagna's modification of periodic acid-Schiff method for glycogen, Feulgen and Rossenbeck stain for deoxyribonucleic acid, methyl green pyronin

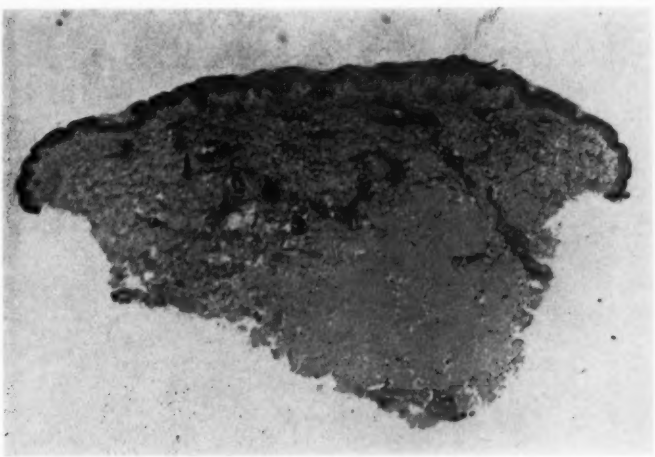

Fig. 1.—Pityriasis lichenoides et varioliformis acuta. Early papule. Low-power magnification shows the entire biopsy tissue. The most striking feature is the marked perivascular infiltrate. Hematoxylin and eosin stain.

for ribonucleic acid, Rinehart-Abul Haj method for acid mucopolysaccharides.

Microscopic Examination

Pityriasis Lichenoides et Varioliformis Acuta.—Twenty-two biopsy specimens were obtained from the eighteen cases of Mucha-Habermann's disease available for our study. All of the characteristic lesions of this condition were included in our material, and the histopathological features of each stage will be described in detail.

(1) Macule (Early): In the youngest lesion to be found in our collection, one only 24 hours in duration, the epidermis is not involved. The scale, the granular layer, and the rete pegs appear normal.

In the corium, however, there are signs of activity. The superficial blood vessels are dilated and engorged with red blood cells. There is a noticeable and marked perivascular infiltrate consisting of lymphocytes. One also sees a small number of red blood cells that have migrated out of the vessels and now occur in the upper corium between the bundles of collagen. The pathologic alterations are similar to those seen in a toxic erythema.

(2) Macule (Scaling): At this stage the epidermis is affected for the first time. The stratum corneum is slightly thickened with a mild but obvious parakeratosis. The granular layer is thinned in some areas and absent in other portions. There is mild to moderate hyperplasia of the epidermis, with a slight intercellular edema.

One of the most striking features is the marked perivascular infiltrate surrounding the vessels in the upper dermis. The cells in this infiltrate are mostly lymphocytic, with an occasional histiocyte. Very important and never described previously in this disease is the invasion of the vessel walls by lymphocytes. In addition, the endothelial cells are swollen, narrowing the lumen of the affected vessels. Although not evident morphologically, diapedesis has occurred, resulting in large numbers of red blood cells located in the dermis just beneath the epidermis.

(3) Papule (Scaling): The epidermis exhibits moderate acanthosis with a loss of rete-peg structure. The horny layer is thicker than usual and contains parakeratotic nuclei. The granular layer behaves in the same manner as described in the scaling macular lesions. A new finding in the epidermis is the presence of large numbers of lymphocytes and red blood cells that have invaded the basal-cell layer and the lower prickle-cell layer.

Just beneath the epidermis there are numerous lymphocytes and red blood cells, with a few histiocytes in a loose edematous corium. Again the most obvious aspect of the entire section is the heavy lymphocytic

Fig. 2.—Pityriasis lichenoides et varioliformis acuta. Necrotic hemorrhagic papule. A large portion of the epidermis is eroded, with a thick scale crust overlying it.

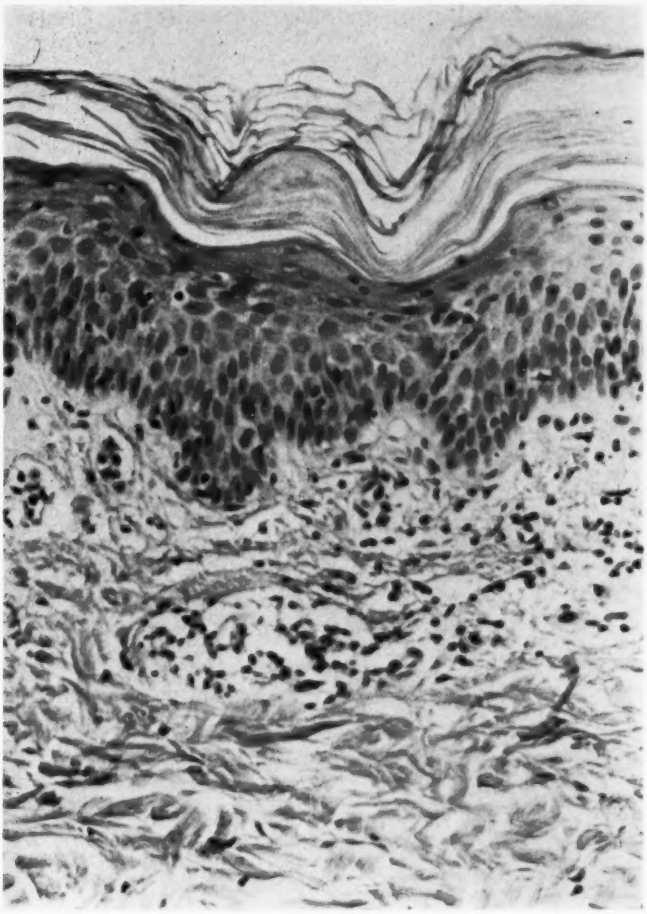

Fig. 3.—Pityriasis lichenoides chronica. Histologic section reveals hyperkeratosis, parakeratosis, and acanthosis. Superficial blood vessels are dilated and surrounded by a mild inflammatory infiltrate. Note that most pronounced changes are in epidermis. Hematoxylin and eosin stain.

mantel surrounding the superficial and even the deep vessels of the dermis. The vessel walls are thickened, with swollen endothelial cells in the upper vessels and hyperplasia of all of the layers in the deeper vessels. Invasion of the vessel walls by inflammatory cells seems to be an integral component of this disease. The pathological alterations involving the vessels resemble the changes seen in secondary syphilis, except for the noticeable absence of plasma cells. It is peculiar, but plasma cells were not found in any of the lesions of pityriasis lichenoides et varioliformis acuta.

A hair follicle within this section is surrounded and invaded by inflammatory cells —mostly lymphocytes and only a few histiocytes.

(4) Vesicle: In this state the epidermal changes are as pronounced as those in the corium and the epidermis loses its normal architecture. An extensive exudative process occurs, characterized by an invasion of numerous lymphocytes and red blood cells into the epidermis, in association with a severe edema abolishing the normal appearance. The epidermis is so densely packed with invading cells that it is difficult to differentiate epithelial cells from inflammatory cells. The upper corium is involved in a similar manner, with a very heavy infiltrate obliterating the border between the

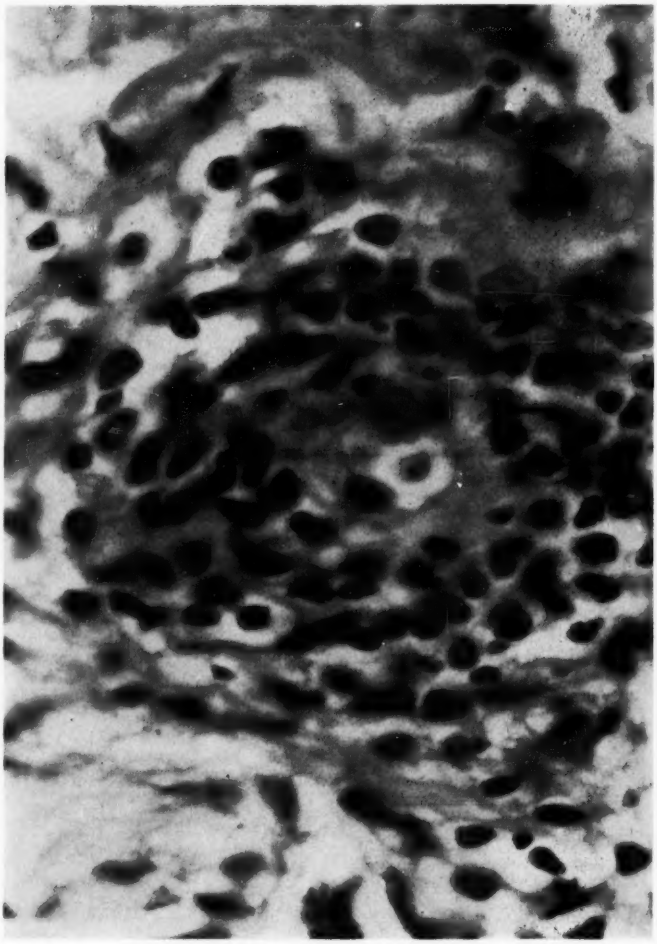

Fig. 4.—Pityriasis lichenoides et varioliformis acuta. High-power magnification shows thickening of all layers of blood vessels, with cells invading the vessel walls. The cells are predominantly lymphocytes, with a few histiocytes. This is the vasculitis characteristic of Mucha-Habermann's disease. Hematoxylin and eosin stain.

epidermis and the dermis. Diapedesis is profuse and seems to be an important feature in all phases of this disease. The superficial and deep vessels show the same changes described for the macular and papular lesions. However, there is a greater proliferation of the vessel walls, leading to complete occlusion in some areas. The skin appendages are not spared from the inflammatory process occurring in this disease.

(5) Necrotic Hemorrhagic Papule: The greatest portion of epidermis is absent with the formation of a large ulcer covered by a thick exudative scale crust. Fibrinous material, keratin, polymorphonuclear leukocytes, lymphocytes, and red blood cells, along with degenerated inflammatory cells, are the components of the crust. The epidermis on each side of the crust shows the same changes seen in the epidermis of the vesicle.

The portion of the corium beneath the ulcer exhibits a marked exudative process, with an extensive red blood cell and lymphocytic inflammatory infiltrate.

All of the blood vessels show the intense vasculitis and perivascular infiltrate so characteristic of other types. Some of the vessels are completely occluded by thrombi or by hyperplasia of the vascular elements.

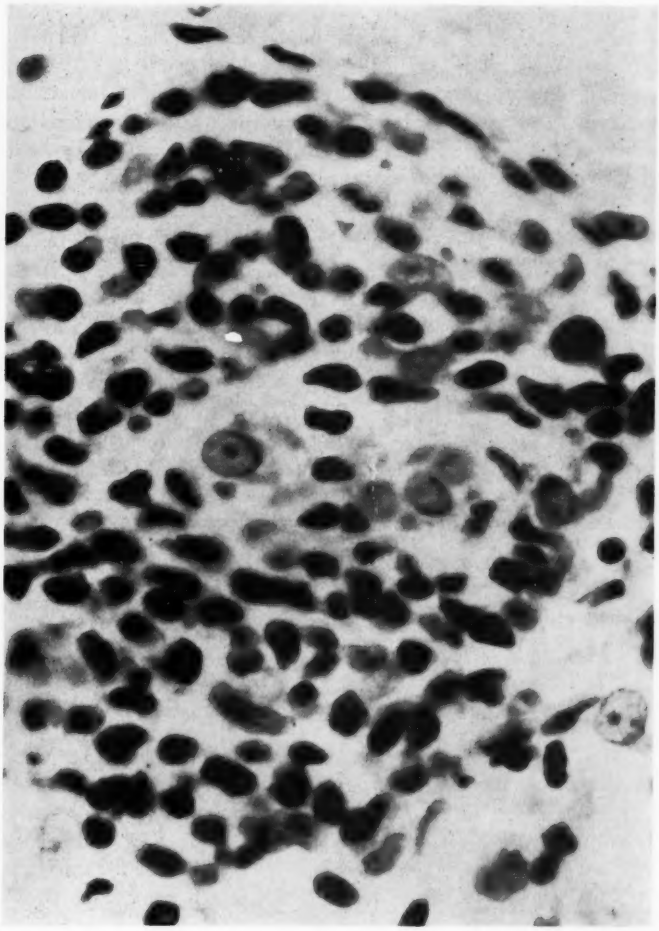

Fig. 5.—Pityriasis lichenoides et varioliformis acuta. Complete occlusion of the blood vessels by proliferation of endothelial cells is noted. Hematoxylin and eosin stain.

Hair follicles, sweat glands, and sweat ducts show inflammatory changes, even to the point of complete destruction. Polymorphonuclear leukocytes are observed amongst the inflammatory cells invading the skin appendages, but again plasma cells are absent.

Pityriasis Lichenoides Chronica

Sections stained with hematoxylin and eosin were studied from 37 cases ranging in duration from 6 months to 14 years. The author was impressed by the astonishingly slight histopathologic changes and by the similarity of many of the sections.

The essential histopathologic changes are located primarily in the epidermis. Usually there is mild to moderate acanthosis, but never as severe as in psoriasis. The horny layer is thicker than normal, and keratotic plugs are noted at times. Parakeratosis is practically always found. The granular cell layer appears to be normal ordinarily but may be thinned or absent in small areas. Intercellular and intracellular edema are always present, and occasionally spongiosis occurs with the formation of vesicles involving the prickle layer and the basal layer. Such vesicles usually contain a small number of lymphocytes. A surprising feature is the presence of frequent mitoses and abnormal cells in the prickle layer in many of the

sections of the Juliusberg type of parapsoriasis.

In the dermis the superficial vessels are usually dilated. A perivascular infiltrate is sparse or moderately heavy. On rare occasions the infiltrate can be profuse. The vessel walls do not exhibit hyperplasia of the individual layers, and invasion of the vessel walls by inflammatory cells is also absent. Lymphocytes seem to be the commonest cells in the infiltrated masses, but a few histiocytes are evident. Plasma cells are not a feature of parapsoriasis in any stage.

Parakeratosis Variegata

This form of parapsoriasis is exceedingly rare, and sections from two cases in which multiple biopsies were done were available in our collection.

Microscopically the scale is thin, with a parakeratosis that must be considered as scanty. The epidermis exhibits a mild hyperplasia, with a loss of rete pegs. Acanthosis is quite regular and even, down to a fairly straight horizontal line. Small abscesses containing lymphocytes and histiocytes are found in the epidermis.

Extending across the upper corium there is a more or less sharply outlined band of inflammatory cells. The infiltrate is made up mostly of lymphocytes and histiocytes, and again there are no plasma cells. The blood vessels appear normal and do not exhibit any thickening of their different layers. Furthermore, the inflammatory cells are distributed diffusely across the upper corium and they are not located perivascularly.

Parapsoriasis en Placques

There is a definite resemblance histopathologically between this member of the parapsoriasis family and parakeratosis variegata.

The scale is thin, with a faint parakeratosis. Acanthosis is mild, and the epidermis is enlarged evenly. Rete pegs are missing. Small groups of cells invade the epidermis, but in this condition histiocytes outnumber the lymphocytes.

The infiltrate occurs as a band more or less in the upper corium. Again there is a preponderance of histiocytes over lymphocytes, and plasma cells cannot be found. The vessels appear normal, and there is no unusual distribution of inflammatory cells around them.

Histochemical Examination

Sections from three cases of pityriasis lichenoides et varioliformis acuta and four cases of pityriasis lichenoides chronica were stained by special methods. The following facts were elicited from this study:

Gomori's Aldehyde Fucsin Stain.—Collagen and elastic tissue stained in a normal fashion. There was no apparent disturbance in the connective tissue in the two entities compared.

Gomori's Reticulum Stain.—No variations in the staining reactions of the reticulum fibers of pityriasis lichenoides et varioliformis acuta and pityriasis lichenoides chronica.

Giemsa Stain.—The study of cells is facilitated by this method. Mast cells are fairly common in all of the sections but more numerous in Mucha-Habermann's disease. Lymphocytes predominate, with a smaller number of histiocytes. The belief that plasma cells are not a part of the inflammation in both diseases is confirmed by the Giemsa stain. Organisms were not demonstrated in any of the sections.

Gomori's Iron Reaction.—Diapedesis of red blood cells into the dermis and epidermis is an important feature of Mucha-Habermann's disease. However, free iron is not evident in this condition or in the Juliusberg type of parapsoriasis.

Periodic Acid-Schiff Method.—There were no fungi in sections from either entity.

Feulgen and Rossenbeck Method.—There was no difference in the staining quality of deoxyribonucleic acid in Mucha-Habermann's disease and pityriasis lichenoides chronica.

Methyl Green Pyronin Method.—Ribonucleic acid stains with equal intensity in all sections.

RSR Method for Sulfhydryl.—No disturbance of sulfhydryl evident in any of the sections.

Bennhold's Congo Red Stain.—Amyloid could not be found in any of the sections.

Periodic Acid-Schiff Method (Montagna Modification).—In the Juliusberg type of parapsoriasis, a heavy deposit of glycogen is found in the upper half of the epidermis, whereas in Mucha-Habermann's disease glycogen occurs in the middle half of the prickle-cell layer. There seems to be a preponderance of diastase resistant substance in the keratin layer of pityriasis lichenoides chronica. There also seems to be a greater number of mast cells in Mucha-Habermann's disease.

Rinchart and Abul Haj Stain.—Acid mucopolysaccharides which stain bright blue were not revealed. A basement membrane, orange-colored, surrounded the sweat glands, but a similar structure was not observed along the base of the epidermis in both conditions.

Comment

Many of the early observers have stressed the histopathological resemblance of pityriasis lichenoides et varioliformis acuta to pityriasis lichenoides chronica. Upon reviewing the histopathological features of the two dermatoses under consideration, one is struck not by the similarity but by their differences.

Mucha-Habermann's disease is essentially a vasculitis with the epidermis involved secondarily. In the earliest lesion, the process resembles a toxic erythema, with all of the changes limited to the superficial vessels. In the early stage and in all phases, the perivascular infiltrate is characteristically and strikingly very heavy. It was this dense collection of lymphocytes and histiocytes surrounding the blood vessels that instigated this investigation. As the lesions advance in age, size, and character the vessel walls thicken, leading to complete occlusion followed by the formation of necrotic lesions. This process of vascular occlusion produces the typical necrotic hemorrhagic papules that are pathognomonic clinically of Mucha-Habermann's disease. A few or many lymphocytes are located in the walls of the involved vessels. The early writers on this subject have described the heavy infiltrate, but there has been no mention of the vasculitis.

Diapedesis of red blood cells is also an integral feature of pityriasis lichenoides et varioliformis acuta. It is noted in all stages, mild in the earliest lesions, then increasing in severity, resulting in many red blood cells located in the epidermis, as well as in the corium. Finally, the well-known hemorrhagic crusted papules are formed almost entirely by a solid mass of red blood cells.

The study of parapsoriasis microscopically is discouraging because there are so few changes that can be considered specific and distinctive. This is not the case in Mucha-Habermann's disease. Civatte in a lengthy review claimed that pityriasis lichenoides chronica is an epidermal disease. Confirmation of this hypothesis is obtained by studying early cases of the Juliusberg type of parapsoriasis. It is apparent that pityriasis lichenoides chronica is a low-grade inflammatory process involving the epidermis primarily. Inflammation involving the superficial vessels of the dermis is minimal or moderate; rarely is it severe. Proliferation of the vascular walls and invasion of the vessel walls by inflammatory cells is never seen in the material available for study. The emphasis in this investigation has been on the comparison of Mucha-Habermann's disease to the Juliusberg type of parapsoriasis. However, in the few cases of parapsoriasis lichenoides and parapsoriasis et placques, there was no resemblance microscopically to pityriasis lichenoides et varioliformis acuta.

A definitive diagnosis of parapsoriasis cannot be made microscopically without benefit of clinical data. However, in the

papular, vesicular, and hemorrhagic lesions of Mucha-Habermann's disease a histopathologic diagnosis can be made objectively when one becomes acquainted with the changes enumerated previously in this article. The combination of the vasculitis, the perivascular infiltrate, the diapedesis of red blood cells into the corium and epidermis, and the thrombosis of superficial vessels, with the production of a necrotic crust, all add up to the diagnosis of pityriasis lichenoides et varioliformis acuta. There are a few diseases which must be considered in a differential diagnosis. Secondary syphilis exhibits vascular changes and a perivascular infiltrate very similar, except for the presence of plasma cells which are completely absent in Mucha-Habermann's disease. Scholtz reported a case of morphologically typical Mucha-Habermann's disease with histologic changes consistent with a diagnosis of secondary syphilis. The Wassermann and Kahn tests of the blood were negative. All of the discussers were struck by the resemblance to syphilis microscopically, and some doubted the validity of the blood tests, requesting a repeat of the Wassermann and Kahn tests. Allergic vasculitis also must be considered because of the similarity of the vessels in the corium. However, allergic vasculitis is characterized by the presence of eosinophils and polymorphonuclear leukocytes and by the necrosis of the vessel walls. Both of these features are absent in the sections of Mucha-Habermann's disease available to me. A toxic eruption is simulated by the changes seen in pityriasis lichenoides et varioliformis acuta. In the former, proliferation and invasion of the vessel walls by inflammatory cells is never seen.

Ingram claims that pityriasis lichenoides should not be regarded as a form of parapsoriasis. He also states that pityriasis lichenoides et varioliformis acuta and pityriasis lichenoides should be considered as a single entity, distinct from parapsoriasis guttata. All of this is based on morphologic features and clinical behavior not apparent to me.

From the data presented in this paper Mucha-Habermann's disease should be considered as a distinct disease, separate from pityriasis lichenoides chronica and other forms of parapsoriasis. The recognition of vasculitis as a basis for pityriasis lichenoides et varioliformis acuta can be explained by improved staining techniques and also by a better understanding of such pathologic alterations. Just as in pemphigus, many years elapsed before histopathologists recognized the significance of acantholysis and the location of the bulla. An analagous situation may have occurred in Mucha-Habermann's disease, with the vasculitis being the important but unrecognized feature.

Histochemical studies, although interesting, did not detect any consequential differences between the two dermatoses.

By segregating Mucha-Habermann's disease from parapsoriasis one can begin to consider new etiologic factors. With a marked vasculitis as the essential pathologic feature, a toxic process must be considered very strongly. A systemic disorder or disturbance should be responsible for the strange entity known as pityriasis lichenoides et varioliformis acuta.

Summary

On the basis of histopathologic data, Mucha-Habermann's disease should not be considered as a form of parapsoriasis.

The basic and essential histopathologic change in pityriasis lichenoides et varioliformis acuta is a vasculitis, differing from pityriasis lichenoides chronica, which is primarily a disease of the epidermis.

With the data presented, it is possible to make a histopathologic diagnosis of Mucha-Habermann's disease objectively.

55 E. Washington St.

BIBLIOGRAPHY

Crawford, S.: Pityriasis Lichenoides et Varioliformis Acuta, Arch. Dermat. & Syph. 26:990, 1932.

Diasio, F. A.: Pityriasis Lichenoides et Varioliformis (Habermann), Arch. Dermat. & Syph. 24:72, 1931.

Gross, P.: Pityriasis Lichenoides et Varioliformis Acuta, Arch. Dermat. & Syph. 23:33, 1931.

Ingram, J. T.: Pityriasis Lichenoides and Parapsoriasis, Brit. J. Dermat. 65:293, 1953.

McCarthy, L.: Differential Diagnosis of Parapsoriasis, Arch. Dermat. & Syph. 45:81, 1942.

Montgomery, H., and Burkhart, R. J.: Parapsoriasis: Its Relation To Mycosis, Fungoides, and Tuberculosis, Arch. Dermat. & Syph. 46: 673, 1942.

Scholtz, M.: A Case for Diagnosis (Pityriasis Lichenoides et Varioliformis Acuta?), Arch. Dermat. & Syph. 27:540, 1933.

Mucha-Habermann Syndrome (Parapsoriasis Varioliformis), Arch. Dermat. & Syph. 30:631, 1934.

Senear, F. E., and Oliver, E. A.: Pityriasis Lichenoides et Varioliformis Acuta (Habermann), Arch. Dermat. & Syph. 23:12, 1931.

Serri, F.: Le parapsoriasi Torino, Edizioni Minerva medica, 1951, Vol. 15.

Wise, F.: Parapsoriasis, New York J. Med. 28:901, 1928.

ABSTRACT OF DISCUSSION

DR. FRANCIS A. ELLIS, Baltimore: Dr. Szymanski has not discussed the clinical features of these two diseases but has adhered to the histologic aspects. He has developed the thesis that histologically the two entities are unrelated by studying in detail the histologic picture in 18 cases of pityriasis lichenoides et varioliformis and compared them with 37 cases of pityriasis lichenoides chronica. Most of us have not had the opportunity to study so many cases of these two relatively rare and infrequent diseases.

On histologic grounds, you would consider parapsoriasis lichenoides chronica to be primarily an epidermal disease. I think that Dr. Szymanski may be a little wrong there. I think that a disease that may look primarily dermal may actually start or have its stimulus in the epidermis and the "toxin" be thrown down into the dermis and cause a visible reaction there first.

He has presented excellent reasons for considering Mucha-Habermann disease as being different from the other forms of parapsoriasis.

Since we cannot usually get multiple biopsy specimens, I wonder at what stage we are often lucky to get one and would it be best to obtain a biopsy specimen in the Mucha-Habermann syndrome?

I am sorry that Dr. Szymanski did not discuss in more detail Dr. McCarthy's article. McCarthy considered the histopathology of parapsoriasis to be rather diagnostic. Unfortunately, we studied this with our cases and we could not agree, and I thought, perhaps, Dr. Szymanski, after his study, might be able to help us.

I wish to congratulate Dr. Szymanski on his research and the presentation of the actual paper, but I am afraid that others may have difficulty in differentiating the histologic picture of pityriasis lichenoides et varioliformis from other severe inflammatory toxic erythematous processes. One must also remember that the type of biopsy and the preparation of the biopsy material are very important factors in the interpretation of biopsies, especially from inflammatory lesions. I think that is one of the troubles where you do not have a special laboratory to do dermatopathology; that is, the general pathologist's technique distorts the picture, and so one has more difficulty in interpreting the histopathologic picture.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I think that Dr. Szymanski is to be congratulated on making clear that Habermann's disease has nothing to do with the guttate form of parapsoriasis, or whatever term you wish to apply to it.

I always followed the teachings of Dr. Oliver Ormsby that Habermann's disease was essentially an acute phase of the guttate parapsoriasis or parapsoriasis lichenoides. My associate, Dr Winkelmann, however, pointed out to me that Habermann's disease was essentially a vasculitis, and, therefore, we are in entire accord with Dr. Szymanski.

The presenter has shown that in Habermann's disease we are dealing with a vasculitis. One might say, not just an arteriolitis but a venulitis, and it is my impression that it may be difficult always to make a diagnosis just on the basis of histologic findings. I thought I saw some necrotizing changes in some of the lesions as depicted on the screen. Obviously, *atrophie blanche* presents an entirely different clinical picture. Vasculitis also occurs in the Lucio phenomenon, which Latapi has so well described as endemic in certain parts of Mexico in certain phases of lepromatous leprosy. Fred Weidman and many since him have described a vasculitis associated with erythema elevatum diutinum, but here the infiltrate is more in the nature of polymorphonuclear leukocytes. One could consider a lot of other vasculitities, including the condition termed by Zeek as allergic angiitis, and also described by the English and by Ruiter as forms of vasculitides. I think correlation of clinical and histopathologic findings is important in all of these conditions.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: I am in complete accord with the view which holds that this entity is distinct from parapsoriasis. Dr.

Szymanski's emphasis on the element of necrotizing vasculitis is well taken and may provide a clue to the nature of the disease. Could this be an anaphylactoid reaction? A recent experience of mine tends to confirm this impression. A young man appeared with an exanthem of two weeks' duration with the characteristic multiform lesions of pityriasis lichenoides et varioliformis acuta. The trunk was particularly involved with all forms of primary lesions, including necrotic pustules. On the forearms, fingers, and toes, purpura was noted. There was no unusual systemic reaction. The histologic picture showed a superficial vasculitis similar to that described by Dr. Szymanski. Treatment in this case was given by means of a series of daily infusions of cortcotropin (ACTH) intravenously for a week. At the end of that time the eruption had cleared remarkably, and the patient has since remained entirely well.

Dr. George C. Andrews, New York: I want to congratulate Dr. Szymanski on his paper and say, from a clinical point of view, that I have been studying a patient with this disease recently, and I am impressed that it is a toxic erythema somewhat like an exanthem. It is one of the exanthemata, probably, and it is not unlike rickettsial pox. I think that it is simply an exanthem of undetermined origin.

Dr. Louis H. Winer, Beverly Hills, Calif.: I wish to compliment Dr. Szymanski for taking this condition out of the group of parapsoriasis. I have not seen a case of parapsoriasis associated clinically with purpura. All cases of Habermann's disease, at some time or other, clinically and histologically, manifest diffuse hemorrhage into the upper cutis. This may be due to vasculitis.

Dr. Wiley M. Sams, Miami, Fla.: Not too long ago, I had occasion to review the three cases of Mucha-Habermann's syndrome that I had observed in a period of 25 years in Florida. On the last local meeting that we held in January, I was unable to attend the clinic, but I sent out Case 4, which I thought was the most typical that I had observed. Within the ensuing two months, I observed a total of six cases and was told that a second case presented at the January clinic was almost, but not quite, as typical as the one which I presented.

Two or three of these patients had eruptions with the typical clinical picture of Mucha-Habermann's syndrome, including the varioliform lesions. The remainder would fall clinically in the parapsoriasis lichenoides chronica group, but they did have the purpuric type lesions, and we came to the conclusion that we were dealing with some type of an exanthematous eruption, perhaps of virus etiology, which has not as yet been fully explained. In a very short time we have thus observed a group of cases of a relatively rare disorder. Dr. Szymanski's histological study indicates that we may obtain additional help for our clinical differentiation of patients with eruptions of this type.

Dr. Frederick J. Szymanski, Chicago: Dr. Ellis states that there might be confusion with a toxic process microscopically. In the main body of the paper I tried to differentiate many entities, among which is a toxic erythema. Mucha-Habermann's disease differs from a toxic process by the invasion of the vessel walls with inflammatory cells in the former and not in the latter. Dr. Montgomery mentions allergic vasculitis as a condition that might be difficult to differentiate from Mucha-Habermann's disease. I feel that the necrosis and invasion of the vessel walls by polymorphonuclear leukocytes is a feature of allergic angiitis and not of Mucha-Habermann's disease.

In answer to Dr. Brunsting, Mucha-Habermann's disease resembles pityriasis rosea, secondary syphilis, and pityriasis lichenoides chronica. This morphologic similarity is part of the reason why Mucha-Habermann's disease is considered as a form of parapsoriasis.

I must agree with Dr. Andrews that Mucha-Habermann's disease has all the appearance of an exanthem. The vascular changes are very similar to those seen in viral diseases and in rickettsial diseases.

Dr. Winer is absolutely correct when he states that purpura is an important feature of this condition. In an early lesion, one only 24 hours old, free red blood cells are seen in the upper corium.

Dr. Sams, the state of Florida must be undergoing an epidemic of Mucha-Habermann's disease. I have never heard of six cases in so short a period. Thank you very much.

Acquired Vascular Tumors of the Skin in the Adult

A Report of Five Unusual Cases

LOUIS H. WINER, M.D., and GERALD H. LEVIN, M.D., Los Angeles

Blood vascular tumors in the adult are a diagnostic and prognostic enigma. Their histologic interpretation also is debatable. These proliferating and recurring vascular tumors clinically are suggestive of neoplasia. Although the majority of these lesions are benign, the possibility of malignancy cannot be overlooked.

The lesions may vary in size from small papules to large tumors. The small papules, which may be red, cyanotic blue, or black, are caused by changes in the most superficial vessels in the cutis. At times there are also changes in the overlying epidermis, such as atrophy, hypertrophy, and hyperkeratosis. The larger lesions involve the capillaries of the midcutis and even proliferate into the subcutaneous fat. Histologically, these vascular tumors differ in the degree of maturation of the proliferating cells. The more mature form lumens, while the less mature form solid cords or masses of cells.

Because of the great variation in clinical, as well as histopathological, appearance, many classifications have been offered with an attempt to combine the various types into groups having proliferation of capillaries as a common denominator. Pathologists have classified these tumors on a histologic basis; clinicians, on a clinical or a clinical and histologic basis.

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From the Medical Service Veterans' Administration Center, General Medical and Surgical Hospital, and the Division of Dermatology, Department of Medicine, University of California Medical Center.

Geschickter and Keasbey[1] grouped these lesions as benign hemangioma, mixed vascular tumor (angiomyoneuroma, or glomus tumor, and angioma associated with squamous- or basal-cell carcinoma), and malignant vascular lesion (metastasizing angioma, primary hemangioblastoma, and Kaposi's hemorrhagic sarcoma).

Stout[2] listed these vascular lesions histologically into two groups, benign and malignant hemangiomas. The benign consisted of capillary hemangioma, cavernous hemangioma, benign hemangioendothelioma, and benign hemangiopericytoma. The glomus tumor, he stated, is the best known variant of the hemangiopericytoma. He placed malignant hemangioendothelioma, malignant hemangiopericytoma, and Kaposi's hemorrhagic sarcoma in the malignant group.

Degos,[3] stating that he was unable to distinguish between vascular nevi and angiomas, classified these tumors first on a histologic basis as cavernous hemangiomas, capillary angiomas, capillary endothelial angiomas, and cellular angiomas. In his clinical classification, which he preferred because it indicated the type of therapy, he included flat angioma (nevus flammeus), stellate angioma (spider angioma, senile angioma, angioma corporis diffusum of Fabry, and angiokeratoma of Mibelli), nodular angiomas, and deep subcutaneous angiomas.

Albertini's[4] histologic classification divided the tumors of capillaries into two groups, benign and malignant, as Stout's did, but with altered terminology and arrangement. In his benign group are hemangioma simplex (capillary hypertrophic

type and cavernous), gemmangioma of Orsos, and lymphangioma simplex. In the malignant group he placed hemangioendothelioma and malignant gemmangioma.

Because of these varied classifications, it is evident that the subject is in a state of confusion.

The most frequent blood vascular tumors which occur in adults are granuloma telangiectaticum (pyogenic granuloma), capillary angioma, capillary eruptive angioma (arterial and venous), glomus tumor, hemangiopericytoma, hemangioendothelioma (angiosarcoma), and Kaposi's hemorrhagic sarcoma.

The granuloma telangiectaticum is usually observed after trauma. It may show histologically only dilated mature capillaries covered by epithelium. Most frequently the epithelium is eroded and absent. Clinically, the tumor appears as a bluish-red, soft, pedunculated, or sessile mass which bleeds on the slightest trauma. This is evident from the histologic structure of the lesion, which consists of three zones: the outer eroded fibrinoid crusted portion, containing polymorphonuclear neutrophils and red blood cells; the middle zone, consisting of solid noncanalized cords of endothelium between which are a few scattered polymorphonuclear neutrophils, and the innermost area, consisting of mature congested capillaries.

The capillary angiomas may be of two types, the hypertrophic and the simple. They may be found together, as in the nevus flammeus, which develops nodules. Microscopically these are composed of mature capillaries and occasionally solid masses of endothelial cells. The connective tissue interstitium is minimal.

The eruptive, or spider angioma involves the capillaries of either the arterial or venous system. The arterial angioma is usually bright red and pulsates on diascopy. Bean [5] stated that the histopathology of this lesion may be of two types: either a simple overgrowth of an end-artery of the skin or a thickened coiled artery in the subcutis. In the walls of the latter are aggregations of glomus cells. These he considered synonymous with the pericytes of Zimmermann or Rouget cells, which Maximow and Bloom [6] consider the precursors of ordinary vascular smooth muscle. Thin-walled, dilated, veinlike vessels, carrying arterial blood to the venous capillaries and collecting system, branch from the coiled artery. The venous type of eruptive angioma is usually blue and overlies a vein which has been obstructed. Although expressible, they refill more slowly than the arterial spider. They may become thrombosed and black, developing "melanomasimulating nodules," as described by Epstein, Novy, Skahen, and Krause,[7] or they may enlarge to form "venous lakes," as described by Bean and Walsh.[8]

This group includes the capillary angiomas due to metabolic disturbance. Angioma corporis diffusum of Fabry clinically shows many punctate diffuse capillary telangiectases and angiomas. Histologically, there is fatty degeneration of the smooth muscle of the arteriolar walls. This progressive postpubescent disorder has been thoroughly described and studied recently by Pittelkow, Kierland, Montgomery, and Schmit [9]; Ruiter,[10] and others. Angiokeratoma of Mibelli is characterized by small red, verrucous, scaly papules most frequently localized on the extensor surfaces of the lower extremities. Histologically, the stratum corneum is hyperkeratotic. The superpapillary plate of the epidermis is atrophic, and the papillary bodies are replaced by large dilated and congested capillaries.

The glomus or neuromyoarterial tumor, described by Masson,[11] is a single painful tumor located on an extremity, usually the finger. It is probably the most frequent histologically studied vascular tumor in the adult. It consists of tangled masses of arterioles which anastomose with aneurysmal-appearing venules. The whole is supported by a framework or capsule of connective tissue and a neural network located in the deeper dermis. The vessel

walls are thick and have within them cells which appear epithelioid, muscular, or ganglionic. They are considered to be modified smooth-muscle cells. Depending on the most dominant structure present, there are four types: the epithelioid, in which the glomus cells predominate; the angiomatous, in which the vessels predominate; the neural, in which nervous elements are in the foreground, and the degenerative, where there are few glomus cells but a well-defined fibrous stroma.

The hemangiopericytoma, first described by Stout and Murray,[12] in 1942, clinically resembles the glomus tumor, except that it is painless. It is a blue or reddish-blue subepidermal nodule. Histologically, it consists of masses of proliferating cells surrounding thin-walled capillaries. The lesion itself is well circumscribed. The cells composing the tumor have large ovoid vesicular nuclei and a pale cytoplasm. On silver staining, the endothelium of the vessels appears as a single layer of cells surrounded by a band of reticular fibers. Peripheral to these are the nests of proliferating pericytes which are latticed by reticular fibers.

Hemorrhagic sarcoma of Kaposi occurs most often on the lower extremity of middle-aged persons. The earliest clinical lesions are telangiectases. Later the lesions become nodular angiomas and, as shown by Ronchese and Kern,[13] involve the lymphatics, as well as the blood vessels. The earliest histologic sections show capillary proliferation, much as one sees it in angioma telangiectaticum or angioma simplex. Older lesions consist of free-lying endothelial cells with extravasated red blood cells, histiocytes containing hemosiderin, and massive fasciculi of fibroblastic connective tissue.

Report of Cases

CASE 1.—A 21-year-old white woman developed eruptive angiomas on the breast during the sixth month of pregnancy. Two weeks after the onset of these lesions, one started to bleed spontaneously. The bleeding was controlled by pressure. This lesion enlarged to 6 mm. in diameter and 4 mm. in height. It was removed six weeks after onset. On the breast above this lesion was one of many smaller angiomas which had developed during her pregnancy. These were arterial pulsating spider angiomas.

The specimen was fixed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin and with silver reticulum stain. The hematoxylin- and eosin-stained section showed hyperkeratosis and atrophy of the epidermal rete due to pressure from below. The capillary nests in the cutis were separated by dense fibrous connective tissue. The individual capillaries seemed to be adjacent to one another and were separated only by a thin layer of endothelium with an interposed thin layer of connective tissue. Solid masses or cords of cells were not prominent. The entire lesion appeared as an organ of vascular structure. The silver-stained section for reticular fibers showed a very thin mantle of reticular fibers around the vessels. There was no increase of these fibers between the vessels. In the connective tissue between the capillaries, the reticular fibers composed a uniform network.

Diagnosis: Benign eruptive hypertrophic capillary angioma (arterial).

CASE 2.—A 62-year-old white woman developed a painful bluish lesion 3 mm. in diameter on the palmar tip of the left second (index) finger six weeks previous to examination. It had become firm and slightly enlarged. She had been on bishydroxycoumarin (Dicumarol) therapy for nine months following a coronary attack. She complained of fleeting intermittent shooting pains in her left arm and forearm. After one of these episodes, she first observed the lesion.

After excision, the tissue was fixed in formalin, embedded in paraffin, and sectioned. The histologic section stained with hematoxylin and eosin showed the epidermis thin and atrophic. The stratum corneum was thin. The upper half of the cutis was replaced by a reticulated cavity, containing numerous septae lined by a single layer of endothelium. This structure originated from a larger vessel in the cutis. The walls of the vessel were undergoing necrosis. Endothelium was proliferating and occluding the lumens of these deeper vessels, even to complete obstruction. Pacinian corpuscles were seen deep in the corium. The reticulum-silver-stained section showed no increase in reticular fibers.

Diagnosis: Venous aneurysm, secondary to bishydroxycoumarin (Dicumarol) or glomus tumor.

CASE 3.—A white man in 1954, at the age of 23 years, first complained of three bleeding lesions on his right forehead. He stated that these lesions, resembling warts, had been removed by curetting three weeks earlier. The wounds bled profusely

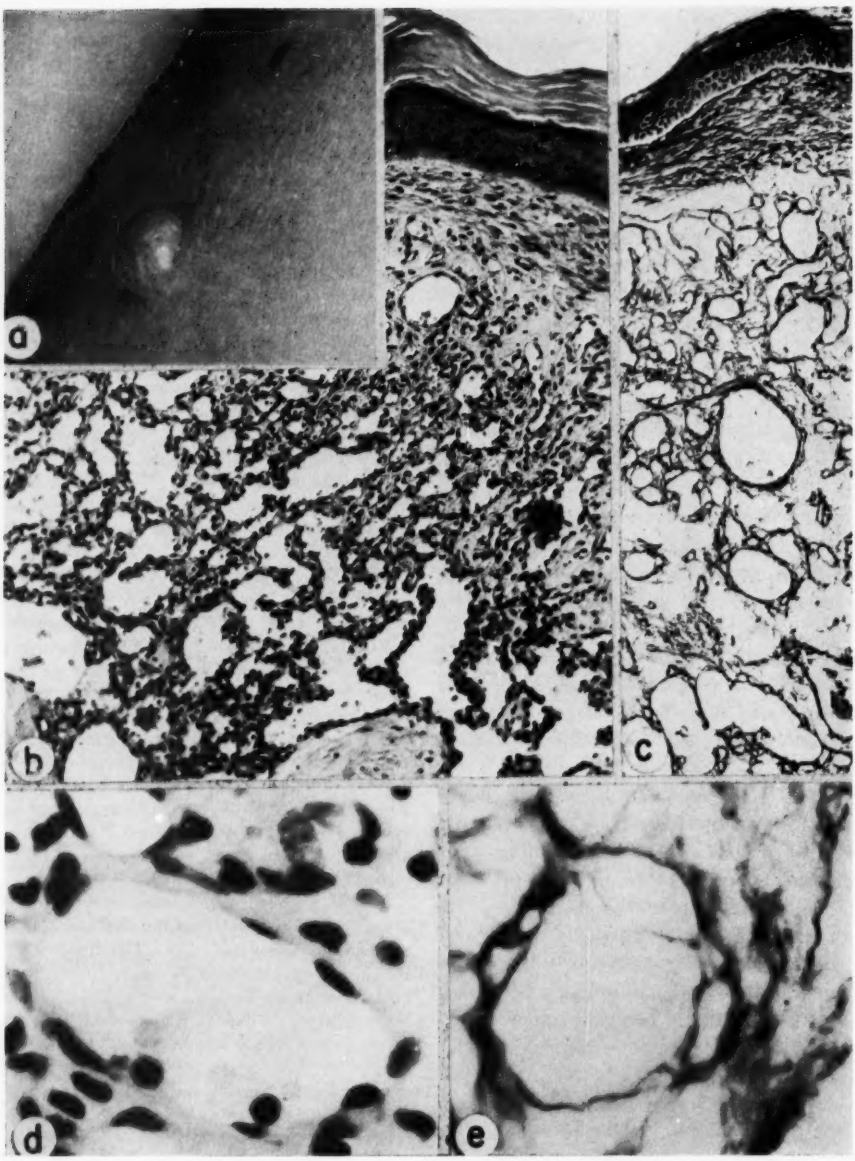

Fig. 1 (Case 1).—Angioma of pregnancy. (*a*) Nodule on the breast with the dark capillary hemangioma above it. (*b*) Vascular spaces lined with mature endothelium. Hematoxylin and eosin; × 140. (*c*) Vascular spaces lined by reticular fibers. Reticulum stain; × 140. (*d*) Mature endothelial cells lining spaces. Hematoxylin and eosin; × 950. (*e*) Thin ring of reticular fibers around the capillary spaces and small amounts in the interstitium. Reticulum stain; × 950.

on the slightest manipulation. These lesions were surgically excised, and the incisions were closed by sutures. They healed by primary intention. Subsequently, he developed more angiomatous lesions on the left forehead, the temples, and on the floor of his left ear canal. A total of 12 lesions have been excised in the past four years. There have been no recurrences at the excision sites. Clinically, these lesions appeared as dome-shaped bluish-red nodules which began as 1 mm.-

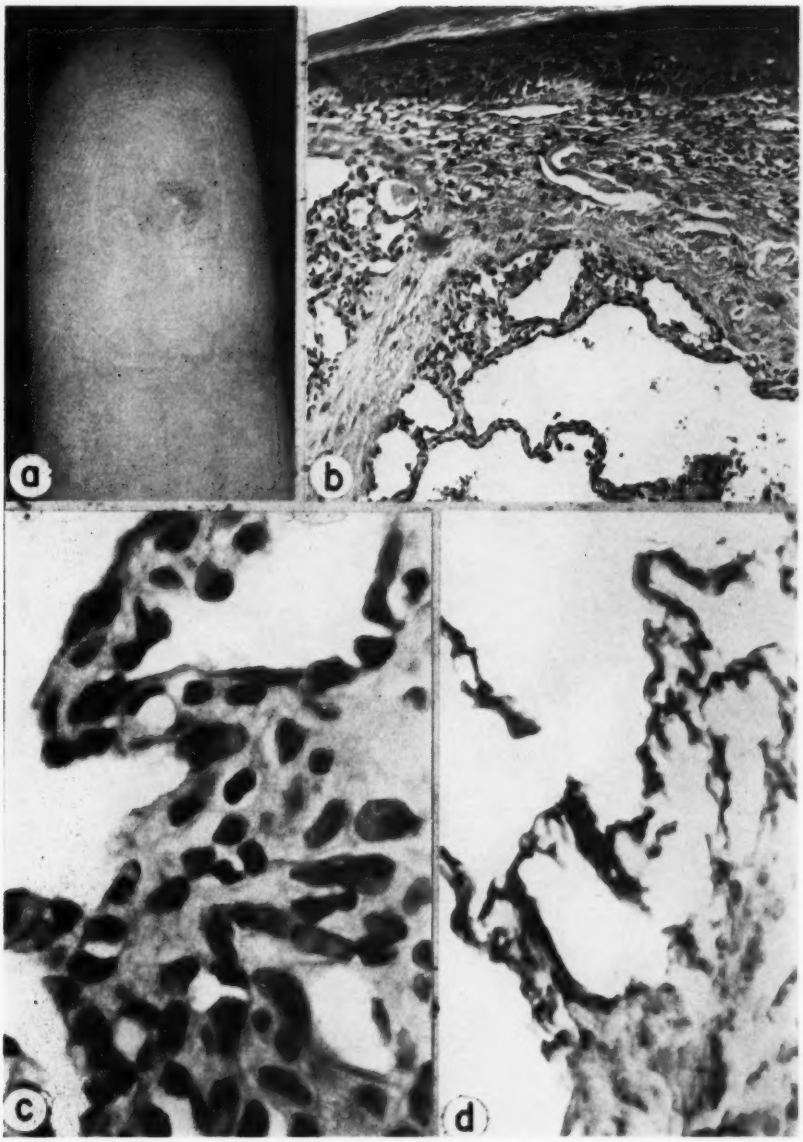

Fig. 2 (Case 2).—Glomus tumor. (*a*) Painful nodule of the finger. (*b*) Endothelial lined mature spaces. Hematoxylin and eosin; × 140. (*c*) Mature endothelial cells. Hematoxylin and eosin; × 950. (*d*) Reticular fibers around the vascular space and in the septae. Reticulum stain; × 950.

sized punctae and rapidly increased to 3 or 4 mm. in diameter and were elevated about 2 mm. There was a sense of pressure at first, but as they increased in size there was no pain.

The excised lesions were fixed in formalin and embedded in paraffin, sectioned, and stained with hematoxylin and eosin and silver reticulum stain. The hematoxylin-and-eosin-stained sections showed, on microscopic examination, that the entire cutis had been involved by sharply circumscribed proliferating masses, consisting of central congested capillaries surrounded by a granulomatous

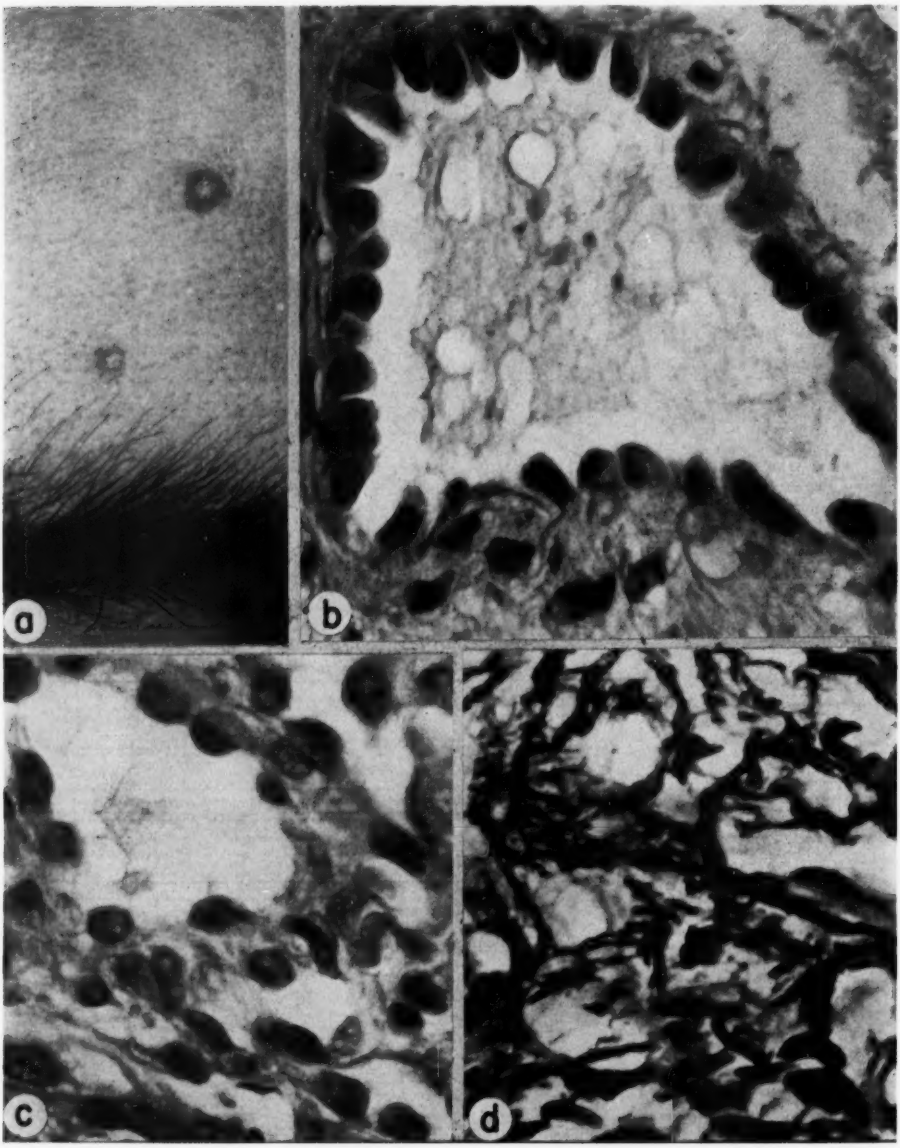

Fig. 3 (Case 3).—Kaposi's hemorrhagic sarcoma. (*a*) Two angiomatous lesions above the eyebrow. (*b*) Acinar endothelium lining vessel. Hematoxylin and eosin; × 950. (*c*) Masses of endothelial cells outside of the vascular lumen. Hematoxylin and eosin; × 950. (*d*) Reticular proliferation of the interstitium. Reticulum stain; × 950.

stroma. The endothelium within the dilated capillaries in the central portion of the tumor was a single layer of columnar cells protruding into the lumen, like tombstone cells. This gave an acinar appearance to these vessels. Surrounding them, the infiltrate was composed of large cells, resembling the endothelial cells which were intermingled with red blood cells. No mitotic figures

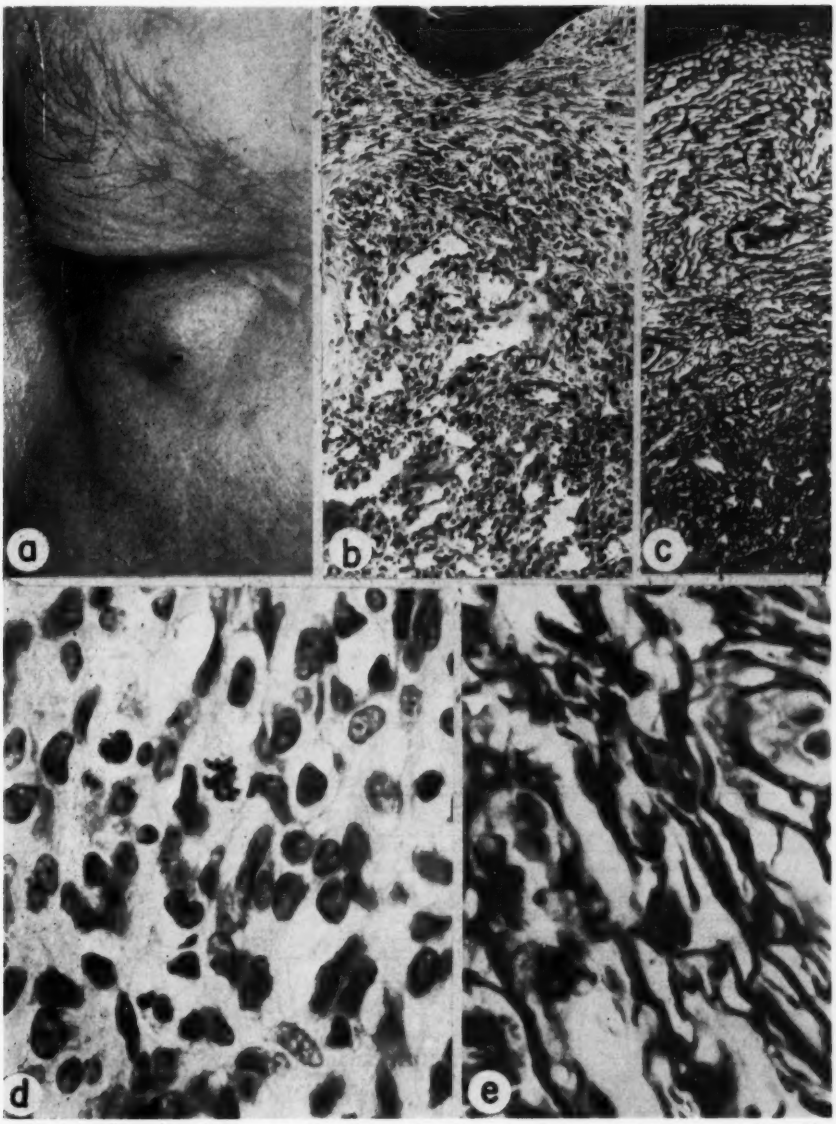

Fig. 4 (Case 4).—Hemangioendothelioma. (*a*) Vascular tumor on the lower eyelid. (*b*) Dense nests of cells in cutis. Hematoxylin and eosin; × 140. (*c*) Intense reticulum proliferation in cellular areas. Reticulum stain; × 140. (*d*) Photomicrograph. Immature endothelial cells, no lumens and mitotic figures. Hematoxylin and eosin; × 950. (*e*) Photomicrograph. Intense reticular fiber proliferation. Capillary lumens contain many endothelial cells. Reticulum stain; × 950.

were seen. Although no peripheral capsule was observed, there was a definite tendency to lobulation.

The reticulum-stained section showed dense masses of reticular fibers surrounding the lumens of the capillaries and the cells surrounding the vessels.

Diagnosis: Idiopathic hemorrhagic sarcoma of Kaposi.

CASE 4 (presented with permission from Dr. William B. Reed).—A 48-year-old white man first noticed a dark red spot, 3 mm. in diameter, on his left lower eyelid in January, 1957. The lesion remained stationary for six months until June,

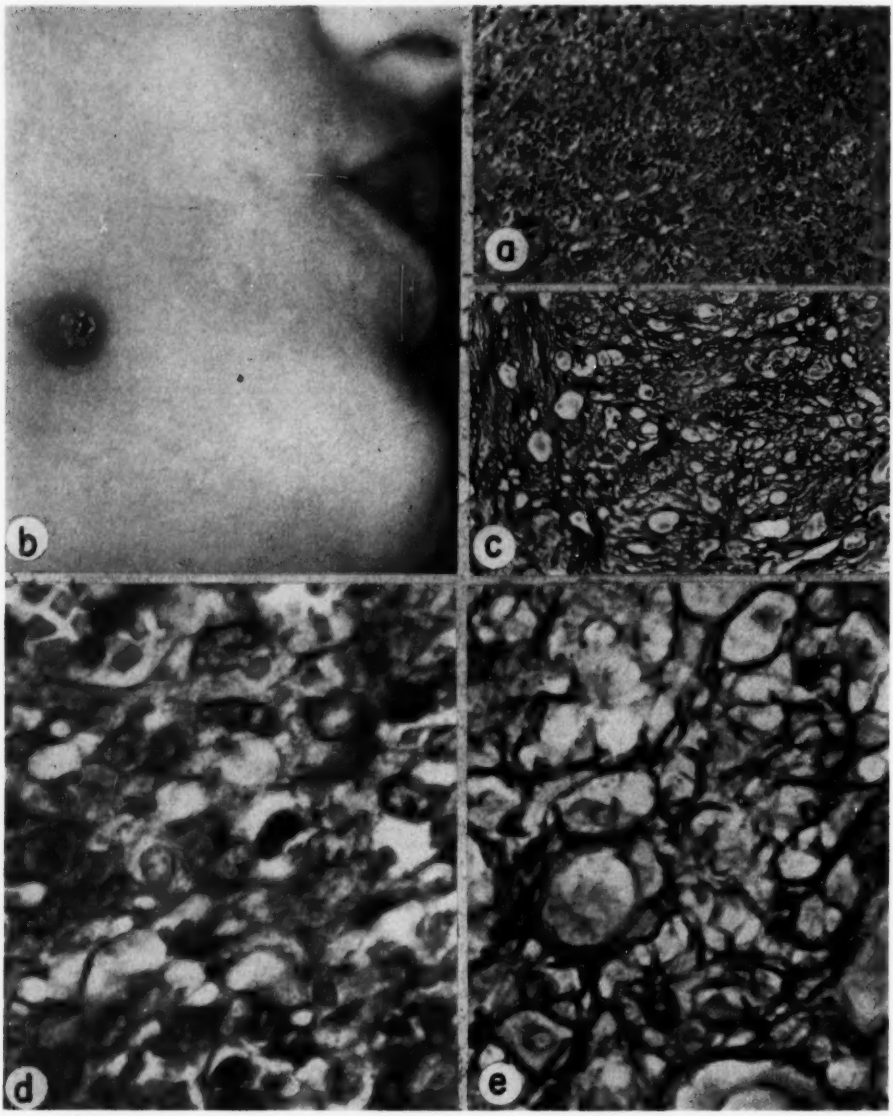

Fig. 5 (Case 5).—Hemangiopericytoma. (*a*) Tumor on right side of chin. (*b*) Compact nests of cells with very small capillaries. Hematoxylin and eosin; × 140. (*c*) Intense reticulum proliferation peripheral to capillary lumens. Reticulum stain; × 140. (*d*) Cells showing neoplasia and degeneration. Hematoxylin and eosin; × 950. (*e*) Increased reticulum formation in the interstitium and surrounding the vessels. Reticulum stain; × 950.

1957, when it grew in diameter and became elevated. He first consulted his physician in October, 1957, at which time a specimen was punched out for biopsy. This was followed by profuse bleeding, which necessitated suturing to control the hemorrhage. Three weeks after this removal, it recurred. It was excised and the base cauterized a second time in November, 1957. Again it recurred. The third time, in December, 1957, it was excised widely.

All three specimens were fixed in formalin, embedded in paraffin, and sectioned. The sections

were stained with hematoxylin and eosin stain and with silver reticulum stain. The hematoxylin-and-eosin-stained sections showed the epidermis to be thin and atrophic, with compression of the ridges by proliferation of a tumor mass in the middle and lower cutis. The tumor consisted of capillary-sized vascular spaces. These were lined by irregular masses of endothelial cells, many of which were undergoing mitosis. The endothelial cells also were proliferating peripherally to the lumens. There was no inflammatory reaction, although free-lying red blood cells were seen. The tumor contained solid masses of large nucleated endothelial cells with vacuolated cytoplasm. At the periphery of the lesion, there is more tendency toward mature luminal formation than in the center of the lesion. Although no fibrous capsule was formed, there was a zone around the proliferating nests of endothelial cells which was clear and appeared to be washed-out and edematous. The lower cutis and subcutaneous fat, as well as the underlying muscles, appeared normal. The silver-stained section showed an increase in the number of reticular fibers. The proliferating cells were seen within the rings of reticular fibers. There was slight intermingling of these cells and fibers.

Diagnosis: Malignant hemangioendothelioma.

CASE 5 (presented with permission from Dr. Edward L. Laden).—A white woman, 25 years old, 6 months pregnant, had a lesion on the skin of the left mandibular area for one year when first seen June 3, 1958. The lesion apparently began without any trauma or previous infection. It had grown very slowly and did not increase more rapidly since she had become pregnant. There had been no bleeding or discharge from the tumor. The lesion was a smooth semiglobular dark red tumor about 1 cm. in diameter, and elevated 3 to 4 mm. above the surface. There was a mild degree of tenderness on palpation. The tumor was surgically excised on Jan. 14, 1958. There has been no evidence of recurrence to the present time.

The specimen was fixed in formalin and embedded in paraffin. Histological sections were stained with hematoxylin and eosin and with reticulum silver stain. The hematoxylin-and-eosin-stained section showed the epidermis to be acanthotic. Large masses of cells intermingled with red blood cells occupied the entire depth of the cutis, down to the subcutaneous fat. Many of these cells were undergoing mitosis. There was much variation in the size and shape of the nuclei of these cells, whose cytoplasm was vacuolated and appeared washed out. The vascular spaces and lumens were lined by a single layer of endothelial cells. Large amounts of hemosiderin were seen in histiocytes on the periphery of the lesion. The silver-stained section showed the entire tumor mass to be interlaced by reticular fibers. These fibers enclosed small capillaries having a single layer of endothelium. The greater proportion of reticular fibers was not circumluminal but located between and around the individual cells of the tumor mass. An occasional mitotic figure was seen between the reticular fibers.

Diagnosis: Hemangiopericytoma.

TABLE 1.—*Classification—Vascular Tumors of Adult*

I. Capillary angiomas			
1. Simple	= flammeus		
2. Proliferative	= capillary-granuloma telangiectaticum		
3. Eruptive	= arterial or venous =	(*a*) Physiologic	
		(*b*) Metabolic	
		(*c*) Traumatic	
4. Cavernous			
II. Glomus types			
1. Epithelioid or glomus cellular with few vessels			
2. Angiomatous (with or without muscle)			
3. Neural			
4. Degenerative			
III. Hemangiopericytoma			
IV. Hemangioendothelioma (angiosarcoma)			
V. Kaposi's sarcoma			

Comment

Clinically and histologically, Case 1 was a hypertrophic capillary angioma. It developed simultaneously with eruptive angiomas during the patient's pregnancy. This lesion belongs in the category of eruptive

TABLE 2.—*Clinical Data*

	Capillary Angioma	Glomus	Hemangio-pericytoma	Hemangio-endothelioma	Kaposi's Sarcoma
Pain	—	+	—	—	—
Consistency	Soft	Soft	Hard	Soft	Soft
Color	Red to black	Blue	Blue	Blue	Blue
Rate of development	Slow	Sudden, rapid	Slow	Slow	Slow
Tend to metastasize	—	—	20%	+	Multiple foci

TABLE 3.—*Histological Data*

	Capillary Angioma	Glomus	Hemangio-pericytoma	Hemangio-endothelioma	Kaposi's Sarcoma
Mature vessels (organoid)	+	+	—	—	±
Endothel. thickened	—	—	—	+	—
Reticular fibers	—	±	+	+	+
Sharp borders	+	+	+	—	±
Fibrous interstitium	+	±	—	—	±
Invasiveness	—	—	+	+	+
Mitotic figures	—	—	±	+	—
Extravasation of blood	—	—	±	+	+

arterial angiomas described by Bean. The reticulum-stained section showed normal numbers of reticular fibers. Although histologically this is a benign angioma, clinically, because of the rapid increase in size, one must consider the possibility of malignancy. Metastases from benign angiomas in adults have been discussed by a number of writers, among whom were Borrmann,[14] Shennan,[15] Ewing,[16] Geschickter and Keasbey,[1] and Robinson and Castleman.[17] Touraine and Duperrat [18] collected 10 additional cases of metastasizing benign hemangioma and decided that the clinical prognosis and the histologic endothelial proliferation warranted the diagnosis of these cases as angiosarcoma. In Robinson and Castleman's case the primary lesion on the breast was histologically benign, but the metastatic tumor in the scalp was malignant. Stout [2] reviewed these cases in detail and concluded that the primary lesions, as well as the metastases, were malignant hemangioendotheliomas.

Case 2 had the clinical characteristics of a glomus tumor; it was located on the finger, was bluish-colored and excruciatingly painful with shooting pains up the arm (might have been anginal), and had a very sudden onset. Histologically, the confusing element was the presence of dilated endothelium-lined spaces with septae-like processes of endothelium extending into the vascular lumen. It suggested a venous aneurysm. Geschickter [19] referred to these numerous infoldings of the vascular walls in his description of glomal tumors. Large amorphous fibrotic masses surround these vascular cavities, and Pacinian corpuscles are prominent beneath the entire process in many sections. This case was presented to the Clinico-Pathologic Conference of the American Academy of Dermatology on Dec. 11, 1957. After examination by 13 dermal and general pathologists, 8 classified this as a glomus tumor and 5 as an angioma with endothelial proliferation. Due to the deficiency in glomus cells and the slight amount of fibroblastic tissue with degeneration, this represents the fourth type of glomus tumor in Masson's classification. With only a preponderance of angiomatous tissue, one is led to a diagnosis of hemangioma and forgets the clinical picture of the glomus which this case presented.

Case 3 presented the problem of a patient with 12 successive angiomatous lesions appearing in a period of four years on the forehead, temple, and external auditory canal. Clinically, the frequent recurrence suggests malignancy. Histologically, except for the acinar-arranged endothelial cells within the lumen of the vessels, there are no stigmata of malignancy. An increase in endothelial cells within the granulomatous areas with interspersed red blood cells is seen. At the American Academy of Dermatology Clinico-Pathologic Conference, Dec. 11, 1957, there was a definite division of opinion. Twelve dermal and general pathologists studied these sections and offered an opinion: Six diagnosed hemangioma; four, Kaposi's hemorrhagic sarcoma, and two, pericytoma. Because of the granulomatous elements, new-vessel formation, endothelial proliferation, and separation plus the great number of reticular fibers, we consider this an example of

Kaposi's sarcoma. Clinically, this is substantiated by the fact that the patient produced new lesions. The lobulation of histologic process and the increase in reticular fibers are indicative of common involvement of the fibrous connective tissue and the endothelial tissue. This indicates the close relationship between a pericytoma and Kaposi's hemorrhagic sarcoma. These had been misdiagnosed because the earliest lesions in Kaposi's show endothelial and capillary arrangement, not unlike that seen in capillary angioma or in granuloma telangiectaticum.

In Case 4, clinically prominent was the frequent recurrence of the tumor and histologically the great number of abnormal mitotic figures seen in the endothelium. The silver-stained section showed a ring of reticular fibers surrounding the vessels within which were proliferating endothelial cells, but no reticular fibers were seen. In addition, the presence of intraluminal endothelial mitoses led to the diagnosis of malignant hemangioendothelioma.

The patient in Case 5 had a slow-growing tumor on the lower left mandibular area for one year, not indicative of malignancy. Histologic section of the biopsy specimen, and the lesion itself after excision, showed solid masses of cells surrounding capillaries. In addition to cellular proliferation, vacuolar degeneration of the cells was evident. Upon staining with silver stain, dense reticular fibers surrounded and intertwined with the individual proliferating cells which were peripheral to the capillary walls and their surrounding reticular fiber rings. This extravascular proliferation of reticular fibers produced by the pericytic cells, and the presence of mitotic figures within the mesh of the reticulum, supported the diagnosis of hemangiopericytoma.

Murray and Stout [20] found that both glomus and pericytoma in tissue culture produced the same cell, the pericyte as described by Zimmermann.[21] In the clinical differential diagnosis, the hemangiopericytoma causes no pain and is large in size and of slow growth, whereas the glomus tumor is a painful lesion, is small in size, and is of sudden occurrence. Histologically, the hemangiopericytoma contains no nervous tissue, has no organoid arrangement, is infiltrative in character, and consists of a coalescent nest of elongated spindle-shaped contractile cells. On the other hand, the glomus tumor always has nerve tissue, an encapsulated or sharply bordered organoid arrangement resembling a blood vessel, and the peripherally dispersed glomus cells are rounded and noncontractile. Metastases have occurred in 20% of hemangiopericytomas, but no metastases have been reported from glomus tumors. Although both are usually solitary tumors, Saunders and Fitzpatrick [22] reported a case of multiple hemangiopericytomas and quoted Stout, who said that it had occurred twice in 200 cases which he had studied.

There are apparently several types of reticular fibers. Jackson and Williams [23] have shown that there are two kinds of reticular fibers in the skin: those surrounding the vessels and partaking in the formation of the epidermal cutis junction and those due to inflammatory or proliferating reactions. Montagna [24] stated that the reticular fibers are immature connective tissue fibers. This agrees with Gross,[25] who stated that on electron microscopy the collagenous and reticular fibers were similar and that the reticular fibers of the young rat formed collagen fibers on aging.

These reticular fibers are argyrophilic and reduce ammoniacal silver nitrate, which stains them black. They are reactive to periodic acid-Schiff stain, which stains them red. They stain poorly or not at all with connective tissue stains. With aniline dye stains, they stain like collagenous fibers. Most observers are of the opinion that reticular fibers are precollagenous elements and not a separate type of fiber. The fibroglia of mesenchyme have the properties of reticular fibers, and these are replaced by collagenous fibers as the tissues grow older.

Orsós observed solid cords or tubes sprouting from the capillaries into an unstained ground-substance-like tissue which might have been reticulum or immature collagen. He termed this gemmangioma, or sprouting-budding angioma.

Helwig [27] differentiated the glomus tumor from the eccrine spiradenoma by the intimate association of reticular fibers to the glomus cells, which is not seen in the latter. He meant that the compact type of glomus tumor, consisting predominantly of epithelioid or glomus cells, produces reticular fibers similar to the pericytes in hemangiopericytoma. In the vascular, neural, and degenerative types of glomus tumor, the reticular fibers are not increased and are closely related to the vascular lumens as in normal tissue.

Histogenetically, the site of origin of these proliferating vascular elements is questionable. Do they arise from embryonal mesenchyme in the tissues or from the endothelium of the vessels? Different tumors surrounding the vascular tree apparently arise from variable sites. Therefore, there is primary proliferation of vascular structure and secondary proliferation of vascular structure. In inflammatory conditions, the vascular proliferation is secondary to the inflammation. In metastatic neoplasms, the vascular proliferation is secondary to the tumor. In hemangioendothelioma, glomus tumor, and pericytoma, however, the primary lesion is in the vascular elements.

Granuloma telangiectaticum or pyogenic granuloma has clinically been confused with melanoma, metastatic hypernephroma, primary squamous-cell carcinoma (especially of the lip), eccrine poroma, Kaposi's hemorrhagic sarcoma, and myxosarcoma. Histopathologically, its diagnosis is usually very simple. However, when involved with other neoplasms (such as squamous-cell carcinoma, eccrine poroma, or hypernephroma), it is difficult to differentiate this lesion from its counterpart, which is secondary to a neoplasm involving another tissue. Because the simplest of these angiomas can be confused with other conditions, it is much more likely that the more complex vascular tumors require greater diligence in their differential diagnosis. For this reason, it can be readily understood why many have diagnosed pericytoma as a reticulum-cell sarcoma, histologically, because the reticular fibers were so prominent. However, the clinical course, its tendency toward benignity rather than malignancy, has warranted consideration of this tumor as an entity.

Summary and Conclusions

Five patients with unusual vascular tumors have been studied.

An attempt is made to unify the classification of vascular tumors.

The diagnosis of a vascular tumor is based on both clinical and histopathologic findings.

Histopathologic sections must be stained with both hematoxylin and eosin and silver reticulum stain to differentiate the intraluminal from the extraluminal proliferation and the association of both.

The histologic sections of eruptive angioma of pregnancy and glomus tumor show simple endothelial proliferation forming mature vessels.

The case of Kaposi's hemorrhagic sarcoma microscopically show immature vessel formation with endothelial and perivascular proliferation.

Endothelial proliferation may be followed by perivascular reaction, as seen in Kaposi's hemorrhagic sarcoma. The lysed endothelial cells invade the surrounding connective tissue and give rise to the resultant granulomas and fibrosis.

The section from the case of hemangioendothelioma shows immature vessel formation accompanied by intraluminal proliferation of cells.

The malignant tumors previously called angiosarcoma are better called hemangioendothelioma because of the intraluminal

proliferation of endothelial cells associated with mitotic figures.

The microscopic sections of hemangiopericytoma show very slight tendency toward vessel formation, with predominance of pericytes and associated reticular fibers.

William L. M. Martinsen, F.B.P.A., helped prepare the photographic and photomicrographic illustrations.

9915 Santa Monica Blvd., Beverly Hills, Calif.

REFERENCES

1. Geschickter, C. F., and Keasbey, L. E.: Tumors of Blood Vessels, Am. J. Cancer 23:568-591, 1935.

2. Stout, A. P.: Seminar on Tumors of the Soft Tissues, Atlas of Tumor Pathology, Washington, D. C., American Society of Clinical Pathologists, 1953, Section II, Fascicle 5, p. 47.

3. Degos, R.: Dermatologie, Paris, Éditions Médicales Flammarion, 1953, p. 767-769.

4. von Albertini, A.: Histologische Geschwulstdiagnostik, Stuttgart, Georg Thieme Verlag, 1955, p. 366-382.

5. Bean, W. B.: The Arterial Spider and Similar Lesions of the Skin and Mucous Membranes, Circulation 8:117-129, 1953.

6. Maximow, A. A., and Bloom, W.: A Textbook of Histology, Ed. 5, Philadelphia, W. B. Saunders Company, 1948, p. 232.

7. Epstein, E.; Novy, F. G.; Skahen, R. A., and Krause, M. E.: Melanoma-Simulating Nodules Due to Capillary Aneurysms, California Med. 85:22-25, 1956.

8. Bean, W. B., and Walsh, J. R.: Venous Lakes, A. M. A. Arch. Dermat. 74:459-463, 1956.

9. Pittelkow, R. B.; Kierland, R. R.; Montgomery, H., and Schmit, R. W.: Polariscopic and Histochemical Studies in Angiokeratoma Corporis Diffusum, A. M. A. Arch. Dermat. 76:59-64, 1957.

10. Ruiter, M.: Das Angiokeratoma corporis diffusum-Syndrom und seine Hauterscheinungen: Übersicht und eigene Erfahrungen der letzen zehn Jahre, Hautarzt 9:15-19, 1958.

11. Masson, P.: Traite de Pathologic Médicale et de Therapeutique Appliquée, Paris, A. Malpine et Fils, 1923, Vol. 27, p. 164.

12. Stout, A. P., and Murray, M. R.: Hemangiopericytoma, Ann. Surg. 116:26-33, 1942.

13. Ronchese, F., and Kern, A. B.: Lymphangioma-like Tumors in Kaposi's Sarcoma, A. M. A. Arch. Dermat. 75:418-427, 1957.

14. Borrmann, R.: Metasenbildung bei histologisch gutartigen Geschwülsten (Fall von metastasierendem Angiom), Beitr. path. Anat. 40: 372-392, 1906.

15. Shennan, T.: Histologically Non-Malignant Angioma with Numerous Metastases, J. Path. & Bact. 19:139-154, 1914.

16. Ewing, J.: Neoplastic Diseases, Ed. 5, Philadelphia, W. B. Saunders Company, 1940, p. 223-233.

17. Robinson, J. M., and Castleman, B.: Benign Metastasizing Hemangioma, Ann. Surg. 104:453-459, 1936.

18. Touraine, A. and Duperrat, R. B.: Les angiomes tumeurs évolutines (essai de synthesis) Ann. dermat. et syph. 9:545-568, 1938.

19. Geschickter, C. F.: Glomal Tumors (Glomangioma or Angiomyoneuromas), Int. Clin. 2:1-12, 1936.

20. Murray, M. R., and Stout, A. P.: The Glomus Tumor: Investigation of Its Distribution and Behavior and the Identity of Its "Epithelioid" Cell, Am. J. Path. 18:183-203, 1942.

21. Zimmermann, K. W.: Der feinere Bau der Blutkapillerin, Ztschr. Anat. 68:29-109, 1923.

22. Saunders, T. L., and Fitzpatrick, T. B.: Multiple Hemangiopericytomas: Their Distinction from Glomangiomas (Glomus Tumors), A. M. A. Arch. Dermat. 76:731-734, 1957.

23. Jackson, D. S., and Williams, G.: Nature of Reticulin, Nature, London 178:915-916, 1956.

24. Montagna, W.: The Structure and Functions of Skin, New York, Academic Press, Inc., 1956, p. 306-307.

25. Gross, J.: A Study of the Aging of Collagenous Connective Tissue of Rat Skin with the Electron Microscope, Abstract, Am. J. Path. 26: 708, 1950; cited by Angevine, D.M., in Ragan, C., Editor: Connective Tissues, New York, Josiah Macy, Jr. Foundation, 1950, p. 17.

26. Orsós, F.: Gefässsprossgeschwulst (Gemmangioma), Beitr. path. Anat. 93:121-139, 1934.

27. Helwig, E. B., Armed Forces Institute of Pathology: Personal communication to the author, April 21, 1958.

ABSTRACT OF DISCUSSION

Dr. Walter R. Nickel, San Diego, Calif.: As histopathologists, we rely on vascular changes as important contributing evidence in arriving at a diagnosis. The vessel changes in periarteritis nodosa, allergic vasculitis, thromboangiitis obliterans, gangrene, scleroderma, erythema induratum, and other diseases are only part of the over-all picture and may be a secondary reaction dependent on some other pathological change.

Vascular tumors in the present discussion, however, present changes which are independent or primary. The microscopic changes are concerned fundamentally with only two cell types: first, the endothelial cell, and secondly, the pericyte or perithelial cell.

As a working "rule of thumb" one could assume that if the proliferation is chiefly that of the endothelial component, the microscopic picture would be predominately vascular, presenting an angiomatous appearance. If, on the other hand, the change is principally in the perithelial cells, the microscopic picture is that of solid sheets of cells. In the malignant group, these sheets of cells would be designated as having a sarcomatous appearance. In the benign group, the designation is that of an epithelioid or organoid appearance.

These criteria would seem to make the problem ridiculously simple. Dr. Winer, however, has stated that precise diagnosis of some of these lesions is extremely difficult, particularly in the lesions suspected of being malignant. Part of the difficulty arises from the fact that malignant hemangioendotheliomas are rare tumors. The pathologist, therefore, does not see these lesions frequently enough to become familiar with the slight or unusual variations in pattern which require special stains for definitive diagnosis.

Exact criteria for the diagnosis of malignant hemangioendothelioma has been set forth by Stout (*Ann. Surg.* 118:445-464, 1943):

"Formation of atypical endothelial cells in greater numbers than required to line the vessel with a simple endothelial membrane.

"Formation of vascular tubes with a delicate framework of reticulin fibers, and a marked tendency for their lumens to anastomose."

In addition to these, the general pathologists who see the greatest number of these rare lesions speak of "sprouting" or "budding" of the capillaries, which is not prominent in benign angiomas. Likewise, the feature of anastomosis seems to be continuous from vessel to vessel. Even with these criteria there is disagreement on any given case, and the exact diagnosis may depend on the clinical course for the final diagnosis. This is in one sense fortunate because this tumor has about the same bad prognosis as malignant melanoma.

I should like to supplement the microscopic classification which Dr. Winer has shown with a clinical classification which was compiled for teaching residents. The chief consideration here is the prognosis of this group of tumors.

Benign

1. Hemangiomas
2. Eruptive angiomas
   A. Senile angiomas
   B. Spider angiomas
3. Pyogenic granuloma (granuloma telangectaticum)
4. Angiokeratomas (Mibelli, Fordyce)
5. Glomus tumor
6. Hemangiopericytoma
7. Benign hemangioendothelioma?

Relatively benign

1. Hereditary telangectasia
2. Angiokeratoma corporis diffusum universale (Fabry)

Relatively malignant

1. Kaposi's hemorrhagic sarcoma
2. Lymphangio sarcoma (postmastectomy)

Aggressively malignant

1. Malignant hemangioendothelioma (angiosarcoma)

I was particularly happy to have brought to my attention that there are four microscopic varieties of glomus tumor. This is a point which is not generally appreciated. The organoid microscopic appearance of most glomus tumors is a dramatic and distinctive feature, which is difficult to explain considering their origin.

Finally, I wish to thank Dr. Winer for introducing me to a new descriptive word for the cuboidal-appearing cell lining the capillaries in Kaposi's sarcoma, the "tombstone" cell. This adequately describes their appearance, and I shall be happy to use it.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: Fifteen years ago, Dr. A. C. Broders and I used to make a diagnosis of hemangioendothelioma, but on reviewing these cases they did not prove to be malignant. On the other hand, Dr. Caro, Dr. Winer, and I have seen truly malignant hemangioendothelioma or angiosarcoma, whichever term you prefer, and we at the Clinic have also seen cases of hemangiopericytoma.

DR. FRANCIS A. ELLIS, Baltimore: Certainly, the comments on the illustrations show that the dermatologic pathologists and general pathologists have a lot to learn, especially about these vascular tumors. We have a vascular tumor at the Southern Medical Dermatopathology Conference that was reported as being hemangioendothelioma, but even before the case was presented, the patient had died from an angiosarcoma.

How can Stout report 100 cases of hemangiopericytomas, while, at the University Hospital, with over 150,000 biopsies, they could not show us any? In dermatopathology, we have 16,000 biopsies, and we have not uncovered any. After looking at Dr. Winer's sections, I do not think that I can diagnose these, but after studying some slides sent to me by Dr. Thomas Saunders and restudying his and Fitzpatrick's article (A. M. A. ARCH. DERMAT. 76:731 [Nov.] 1957), I think that I now have a clear picture of the histopathology of the usual hemangiopericytomas.

In Kaposi's disease, and in Dr. Winer's case, instead of having the progressive lesions on the legs in older people—in the Russians, Jews, or the Italians—we are seeing more cases in Americans that start with lesions on the face and other

areas about the head. Histologically, they are typical.

DR. ADOLPH ROSTENBERG JR., Chicago: I should like to emphasize a point of some importance which has been brought out this morning, namely, the difficulty of reconciling the pathological appearance with the clinical course of the lesion. This was forcefully brought out to me when I was at the Food and Drug Administration and we were prosecuting a well-known cancer quack of Detroit. One of the cases introduced by the defendant was that of a man who was hit by a baseball and who subsequently developed a swelling over one shoulder. He was sent to University Hospital, Ann Arbor, Mich., where, finally, a biopsy specimen was obtained and a diagnosis of malignant hemangioendothelioma was made. Scapulohumoral disarticulation was recommended. The man said, "The hell with it! I am not going to have it done." He went to the cancer quack and was treated with some injections.

All this occurred about nine years before the trial, and at the time of the trial he was working as a welder in the Willow Run bomber plant. This story wasn't very good for the government's case. I went out to the hospital and talked to Dr. Weller, who had the block recut, and said, "Sorry, but it's a malignant hemangioendothelioma." How or why this man got better, he didn't know, and I don't know. I don't think the cancer quack cured him. I simply think that you cannot always predict what is going to happen from the pathologic picture.

DR. MARCUS R. CARO, Chicago: I am particularly interested in the malignant hemangioendothelioma because that is a condition which, in my experience, is extremely rare. My initial paper before this Association, in 1944, was based on a study of one case of a malignant hemangioendothelioma, and I have not seen another one since that time. In my patient, I was able to verify all of the criteria that were mentioned by Dr. Winer for his histopathologic diagnosis, including the endothelial proliferation, as a result of which the blood vessels were lined by more cells than were necessary, the budding from the walls of the vessels, and, particularly, the vascular anastomoses.

In my own case, and I believe that it is true of other cases seen since that time, the tumor was extremely radioresistant. In spite of the intensive roentgen therapy given at the time, the patient went on to develop metastases and died.

DR. LOUIS H. WINER, Beverly Hills, Calif.: I agree with Dr. Rostenberg that neither the clinical nor the histopathological features alone are diagnostic, but both together must be taken into consideration in order to arrive at the proper diagnosis. Dr. Montgomery and Dr. Broders used the clinical progress to guide their histologic diagnosis of vascular tumors.

It is because of the indefinite histologic criteria that we decided to do this work. We think that hemangioendothelioma is indicative of neoplasia and is a malignant tumor of blood vessels. It is really a sarcoma, rather than a plain adenomatous type of structure, since we find abnormal mitotic figures in the histologic sections. After this article was written, we acquired a new case in a 9-year-old boy where each microscopic high-power field contained four or five abnormal mitotic figures. This, to us, is indicative of a malignant hemangioendothelioma—hemangiosarcoma. There were definite anastomoses of the lumens. The reticulum-stained section of these tumors shows that there are proliferating cells within the lumens.

In answer to the question raised by Dr. Ellis as to why they do not see pericytomas in their department, one may say that many of these lesions are diagnosed reticulum-cell sarcoma because of the great preponderance of reticulum fibers present, as well as by the appearance of the cells themselves. However, the tendency to form lumens lined by single layers of endothelial cells with great amounts of reticulum, which is produced by the pericyte cells, and the tendency of these patients to remain free of metastases or further development of these lesions following their removal favors the diagnosis of a relatively nonmalignant lesion, such as a pericytoma.

Smooth-Muscle Tumors of the Skin

HAMILTON MONTGOMERY, M.D., and R. K. WINKELMANN, M.D., Ph.D., Rochester, Minn.

Smooth-muscle tumors of the skin occur infrequently. We wish to report a series of 33 cases in which such lesions were present. This group is divided into 23 cases of leiomyoma cutis; 8 cases of angiomyoma; 1 case of nodular, or so-called dartoic, myoma, and 1 case of leiomyosarcoma. The occurrence of only one example of nodular, or dartoic, myoma in this series can be explained on the basis that such tumors arise from special rows of smooth-muscle cells in the scrotum, nipple, and external genitalia deep in the subcutaneous tissue and, therefore, are seen primarily by the surgeon for excision. We have been especially interested in this study in regard to why some myomas are painful and some are not. Particular attention was given to use of histochemical techniques to differentiate myomatous tissue from other mesodermal tissues.

Survey of Literature

It is not our purpose to give a complete review of the literature. Ormsby [1] reviewed the data in all the cases reported before 1924. He also emphasized that the painful tumors were the larger lesions, in which the mass pressed on nerves. His classification of myomas was much simpler than some of the other ones in the literature [2-4] and is the same as the one we have employed. More recent reviews on myoma have been given by Stout,[5-7] Jansen [8] and many others.[9-11]

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Section of Dermatology, Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

Some articles have dealt with the etiologic aspects of various myomas of the skin. Nödl,[12] for example, maintained that multiple leiomyomatosis of the skin is a neurocutaneous syndrome. Grzybowski [13] reported a case of cutaneous leiomyoma of the face in which, using Cajal's modified silver-impregnation method, he demonstrated a great many neurites both in and around the lesion, including small nerve bundles of nonmedullated nerve fibrils. He thought that formation of new nerve fibers was present. We have been unable to duplicate these observations. Radermecker and van Bogaert [14] described a case of extensive leiomyoma with general diffuse leiomyomatosis of a nevoid nature, or nevus leiomyomatosis systematicus. Nevoid disturbances of hair follicles and sebaceous glands were present, associated with histopathologic changes of leiomyoma. Sonck [15] supported Radermecker and van Bogaert's point of view; in his case of leiomyomatosis cutis miliaris, in which the patient had about 5000 lesions, he referred to the condition as one of congenital nevus-like mesenchymatous dysplasia, or, in other words, nevus leiomyomatosis systematicus. The patient was especially sensitive to cold and also to heat. Two cases of leiomyosarcoma with lymphatic spread and metastasis to regional lymph nodes were reported by Levack and Dick [16]; other cases have been reported by Ackerman and Stout,[17] and Stout.[6] Such cases apparently are rare, and most of these tumors have not shown metastasis over a period of many years.

Methods and Materials

As already mentioned, a series of 33 smooth-muscle tumors of the skin in which biopsy was done were reviewed. Routine stains included hematoxylin and eosin, Van Gieson's stain, and elastin

TABLE 1.—*Leiomyoma Cutis: Clinical Data in Twenty-Three Cases*

Case	Sex	Age, Yr.	Duration, Yr.	Site	Painful	Clinical Appearance
1	F	48	20	Arm, legs, shoulder	In 3×3 cm. area	Small painless nodules (50)
2	M	32	12	Legs	+	Nodules
3	F	55	1	Chest, shoulder	0	Urticarial plaques
4	F	35	8	Face	Pruritus; no pain	Linear plaque
5	F	42	--	Shoulder, arms	0	Nodules
6	F	41	20	Wrist	0	Nodules
7	M	27	--	Neck	--	Nodules
8	F	50	8	Legs, arms	0	Nodules
9	M	61	43	Shoulder, back, arms	+	Lines and circles
10	F	1	Birth	Left axilla	--	--
11	M	Adult	4-5	--	0	Grouped nodules
12	F	44	20	Left forearm	+	Nodule
13	F	48	Yr. (?)	Back	0	Nodules
14	F	55	Yr. (?)	Chest, forearms	0	Nodules
15	F	53	1/6	Left wrists, forearms	0	Nodules
16	F	32	Yr. (?)	Right arm	+	Grouped
17	F	50	6-10	Back, neck, arm	+ (also pruritus)	Linear & grouped
18	F	51	20	Back, arms, legs	+	Nodules
19 *	M	35	20	Chest, left arm	+	Grouped
20 *	M	43	10+	Left arm, shoulder	+	Grouped
21 *	M	44	Several	Trunk, chest, forehead	+	Grouped
22 *	F	52	Yr. (?)	Chest, hip	+	Grouped
23 *	M	63	Yr. (?)	Arm, thigh	+	Grouped

* Multiple biopsies done in these 5 cases.

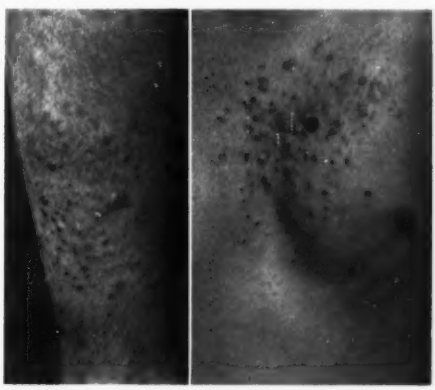
H. It was hoped that more information could be obtained by use of trichrome stains, such as the Mallory-Heidenhain technique, but this did not result. The Gomori resorcin-fuchsin stain for elastic tissue and the Gomori reticulum stain were useful.

Histochemical techniques were applied to the study of this tissue, but without significant success. The Bignardi chromation procedure for the production of carboxyl-dependent metachromasia in smooth-muscle masses was only irregularly successful. The Feulgen technique was noncontributory. Methods for polysaccharides and lipids gave negative results. Because Congo red is reported to have an affinity for muscle tissue,[18,19] this stain was also tried but without success. Other methods included the tetrazolium technique for succinodehydrogenase, the sulfhydryl reaction of Barrnett and Seligman,[20] and the β-glucuronidase reaction of Fishman and Baker.[21] Increased amounts of these materials have been reported in smooth muscle, but study of fresh tissue from leiomyomas was not rewarding. Studies for nerves were done with the Bodian technique. The lesions in three cases of leiomyoma cutis and three cases of angiomyoma were studied with the frozen-section silver method for axoplasm.[22,23]

Leiomyoma Cutis

Clinical Features (Table 1).—Leiomyoma cutis of the skin commences in early life, even in infancy or at birth, according to reports in the literature. The average age of our 23 patients at the time of onset of the clinical signs ranged from 10 to 20 years. The tumor progresses slowly. It soon demonstrates multiple foci of neoplastic activity and appears to have an autochthonous multicentric origin in most cases. It usually has a protracted course. The

Fig. 1.—Leiomyoma cutis. The lesions are on the ankle and lower leg in one case and over the sternum and breast in the other. In each instance, the larger lesions were painful but the smaller lesions were not.



lesions may be located on the face, trunk, or extremities (Fig. 1). The tumor is situated primarily in and fixed to the dermis and usually grows out from the surface of the skin. The grouped nodular lesions may coalesce to form plaques. Arciform or linear aggregations of nodules are characteristic. The lesions usually are red, but hues of yellow and brown may be admixed. The nodules occasionally are glistening or semitranslucent. In one of our cases, telangiectasia accompanied the lesion. In three cases, the lesion was recorded as turning from red to white when pain was elicited. Vermiform movements of the tumor have been recorded but were not present in any of our cases.

Some of the lesions were painful; a comparison between these and nonpainful lesions is presented in a subsequent section. Two lesions were tender when hot, and three were tender when exposed to cold. All painful lesions were tender when mechanically stimulated. Spontaneous pain in a nodule of leiomyoma cutis occurred only once. Pruritus was present in three lesions that were not painful. In one patient, the following events were recorded as accompanying the episode of pain: "The pupils dilated, the patient became pale, and the blood pressure fell. The episode lasted from 15 to 20 minutes."

A family history was obtained in one patient, who stated that her father had similar nodules.

Pathologic Aspects.—Leiomyomas of the skin presumably arise from the arrectores pilorum muscle. The involvement of the dermis by smooth-muscle bands and masses is characteristic of this tumor (Figs. 2 and 3). No capsule or organization exists, especially in superficial nonpainful lesions. The characteristic histologic feature is the appearance of transverse sections of muscle fascicles. The centrally placed nuclei and the regularity of the cellular masses are distinctive. This is reflected in the regular

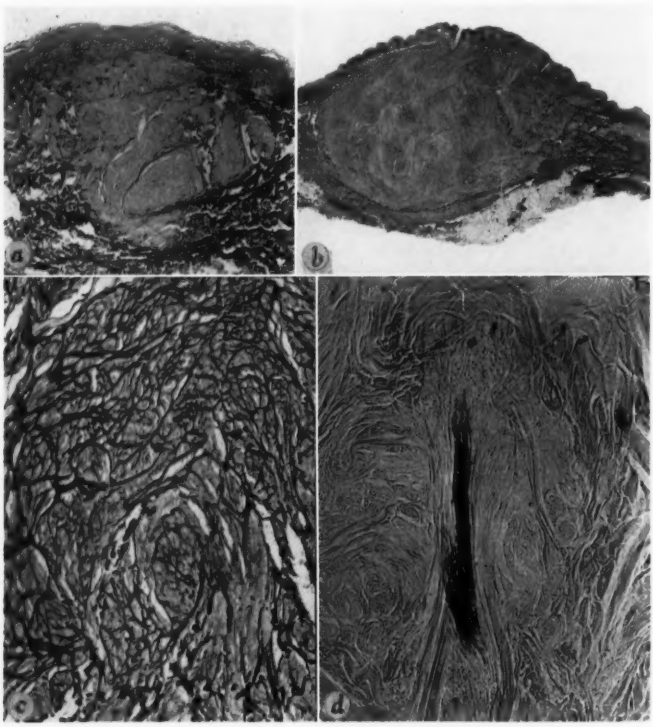


Fig. 2.—Leiomyoma cutis. (*a*) Small superficial painless lesions. Note the zones of normal connective tissue between the masses; Van Gieson; reduced 25% from mag. ×25. (*b*) Larger deeper painful lesion in same case; hematoxylin and eosin; reduced 25% from mag. ×6. (*c*) Gomori reticulum stain in same case, revealing regular pattern of smooth muscles surrounded by organized pattern of fine reticulum fibers appearing black; reduced 25% from mag. ×180. (*d*) Nerve fibers (black) being compressed by smooth-muscle tumor. This was a painful lesion; special stain for nerves; reduced 25% from mag. ×120.

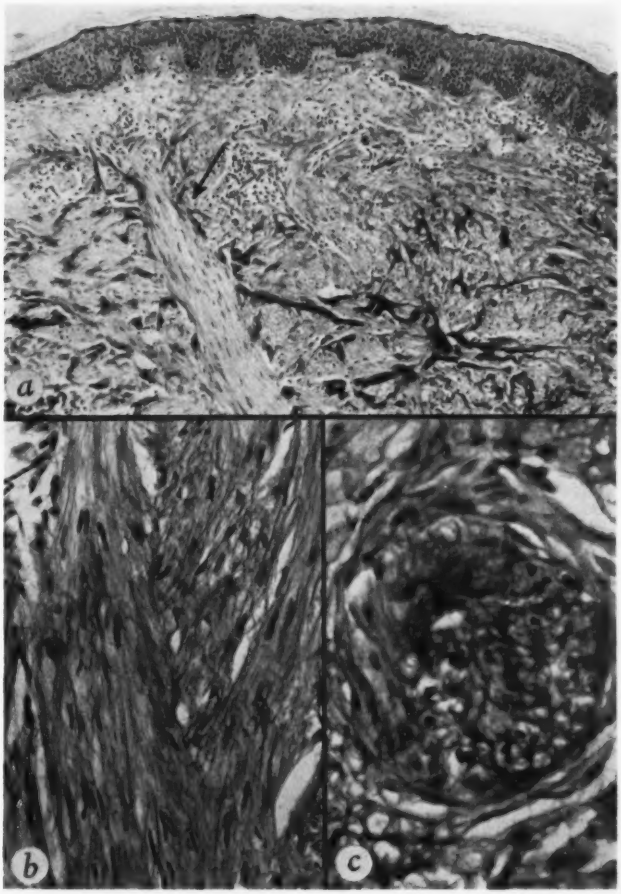


Fig. 3.—Leiomyoma cutis. (*a*) Typical picture of superficial lesion, showing smooth muscle in relation to arrectores pilorum muscle at arrow; Van Gieson; ×75. (*b*) Same case; greater magnification of muscle cells to show myofibrils; Van Gieson; ×245. (*c*) Leiomyoma of a painful nature. Note involvement of cutaneous nerve bundle; Van Gieson; ×435.

connective-tissue pattern even when there appears to be an increase in the connective-tissue stroma. The amount of destruction of elastic tissue varies in different lesions, and often the elastic tissue is merely pushed aside. The reticulum stain demonstrates the regularity of the masses of tumor cells and the surrounding reticulum pattern (Fig. 2[*c*]).

Comparison of Painful and Painless Lesions.—Multiple biopsies were done on painful and painless lesions in five cases. Little clinical difference was apparent except for the size of the lesion; the painful lesions were always larger and more developed. Figure 2(*a*) illustrates a section through a nonpainful nodular lesion. The masses of smooth-muscle tissue are lying loosely in the substance of the dermis; also, it should be noted particularly that the level of the dermis-subcutis border has not been reached. In all painful lesions, the smooth-muscle masses had developed to sufficient size to penetrate the tissue to the level of the panniculus (Fig. 2[*b*]). Usually by this time they also protruded from the surface; while a clear zone separated the epidermis and the tumor in most instances, the epidermis usually showed pressure effects from the encroachment of the dermal lesion.

Studies for nerves disclosed that it was not until the mass of smooth muscle had developed sufficiently to occupy a large

TABLE 2.—*Cutaneous Angiomyomas: Clinical Data in Eight Cases* *

Case	Sex	Age, Yr.	Duration	Site
24	F	61	Recent	Right knee
25	F	47	9 mo.	Left forearm
26	F	31	5 yr.	Left calf
27	F	52	—	Left upper arm
28	F	56	—	Left leg
29	F	70	6 mo.	Popliteal fossa
30	F	59	3 yr.	Left calf
31	F	58	Recent	Right Achilles region

* The tumors were painful in all 8 cases.

volume of dermis that the tumor became painful. In all the painful tumors examined, large nerve trunks were included within the muscle mass itself. In small painless lesions, nerve fibers and trunks were found about the periphery of the tumor, as if the invading tumor had pushed the nerve to one side rather than including the nerve between the smooth-muscle fascicles. In a blind evaluation of the lesions in given cases of leiomyoma cutis, it was found possible on study of sections stained by hematoxylin and eosin for one of us (R. K. W.) to tell accurately whether histologic sections came from painful or painless lesions. This selection was based solely on the amount of dermis involved and the level in the dermis to which the tumor had penetrated.

Angiomyoma

Clinical Features (Table 2).—Angiomyoma arises in the deeper portions of the dermis or the subcutaneous tissue and presents as an isolated flesh-colored or blue nodule on the extremities. All of our eight patients were women. The pain that was common to all these lesions and the relatively short course are deserving of notice. The lesions arose late in life in all eight patients and were generally painful within three years; symptoms were noted usually by the

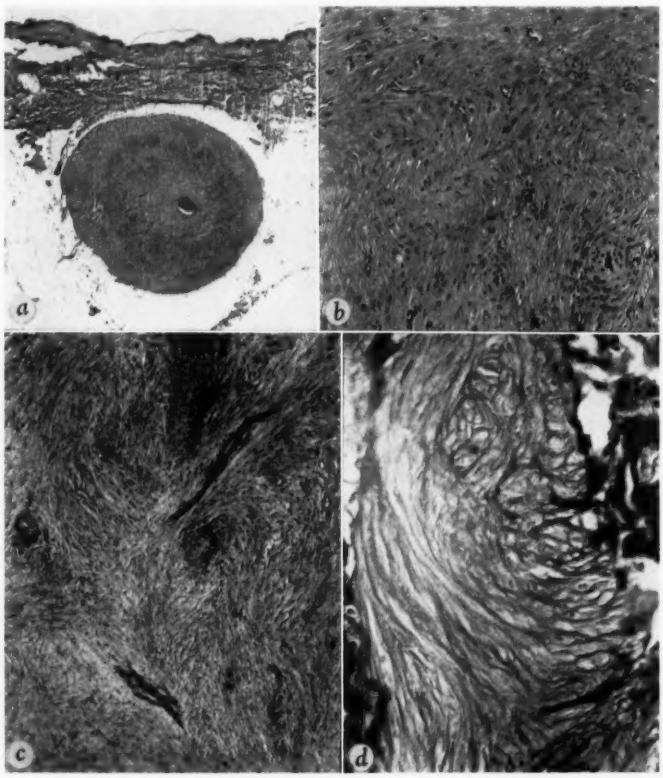


Fig. 4.—(*a*) Solitary angiomyoma in left upper arm. Tumor lies deep in cutis and subcutaneous tissue; hematoxylin and eosin; reduced 25% from mag. ×10. (*b*) Angiomyoma from right knee, revealing small vessels; hematoxylin and eosin; reduced 25% from mag. ×100. (*c*) Angiomyoma from right knee, showing nerve bundles (black) being compressed by tumor cells; special stain for nerves; reduced 25% from mag. ×165. (*d*) Nodular (dartoic) myoma from scrotum. Note smooth-muscle cells in both longitudinal and cross section; Van Gieson; reduced 25% from mag. ×325.

end of the first year. The presence of pain brought the patient to the physician in most instances. Pruritus was absent. Changes in temperature did not induce pain. In many instances, the pain was spontaneous, as well as mechanically induced.

Pathologic Aspects.—Angiomyomas apparently arise from the tunica muscularis of blood vessels. These tumors are rounded masses of smooth muscle found usually below the dermis (Fig. 4[*a*]). Masses of capillaries and medium-sized blood vessels are seen within the tumor (Fig. 4[*b*]). An elastic-tissue stain is helpful in this tumor in outlining the internal elastic lamella and demonstrating the vessels even in a tumor that may show some degenerative signs. Figure 4(*c*) shows a pair of nerve trunks included within the substance of an angiomyoma. These tumors are painful early in their development, principally because somatic nerves accompany small vessels into the tissue and are found mingling with autonomic fibers in the adventitia of the vessels. Therefore, sensory fibers are caught by a tumor developing in the vessel wall and pressure is exerted early on the deeper nerve trunks that usually accompany vessels in the septa of the panniculus.

Nodular (Dartoic) Myoma

Clinical Features.—The nodular myoma in our series was from a 54-year-old man who had noted a symptomless solid semitranslucent 2 cm. mass on his scrotum for years. The patient desired removal of this tumor, and accordingly it was taken off as an excision biopsy. The clinical diagnosis was epidermal cyst. Examination disclosed a smooth-muscle tumor arising in the dartos tunic of the scrotal tissues.

These smooth-muscle masses generally are solitary, may occur at any time of life and are usually not painful. The lack of pain is probably due to their origin deep in the subcutaneous tissue; they push the nerve trunks aside rather than growing around and about the nerve trunks and compressing them. The true diagnosis is discovered only on removal at the patient's request, as in this instance.

Pathologic Aspects.—The pathologic features of nodular myomas are similar to those of leiomyoma cutis. Figure 4 (*d*) shows a smooth-muscle mass representative of the histologic picture of this type of tumor.

Leiomyosarcoma

Clinical Features.—As already noted, our series of 33 cases included 1 instance of leiomyosarcoma. A 32-year-old woman noted an extremely tender nodular lesion on the right thigh in 1937. It had bled on two occasions when it had been traumatized. It was approximately 1 cm. in diameter and was elevated 0.5 cm. above the surface of the skin. It was fulgurated, but it recurred. On the second occasion, it was treated with a half-strength radium plaque for 20 minutes, but it did not respond adequately. It was excised, and the original impression of granuloma telangiectaticum was proved to be erroneous when a leiomyosarcoma was discovered.

Fourteen years later, the patient was found to have a small painful nodule on the perineum of unknown duration that was thought to be either a Bartholin cyst or a glomus tumor. The latter diagnosis was made at the time of excision, but recent review of the sections made it appear more likely that the lesion was a hemangiopericytoma rather than a glomus tumor. The patient, when seen clinically in January, 1958, which was 21 years after excision of the leiomyosarcoma of the thigh, apparently had no recurrent tumors.

As far as we know, this is the only case of cutaneous leiomyosarcoma that has been seen at the Mayo Clinic. Probably not more than a dozen cases of cutaneous leiomyosarcoma have been reported. These tumors are extremely rare and usually remain localized, although Levack and Dick reported two cases of cutaneous leiomyosarcoma with lymphatic spread, as already noted. Dr. Dick and Dr. John Milne, of Ayrshire, Scotland, made available tissue from the second

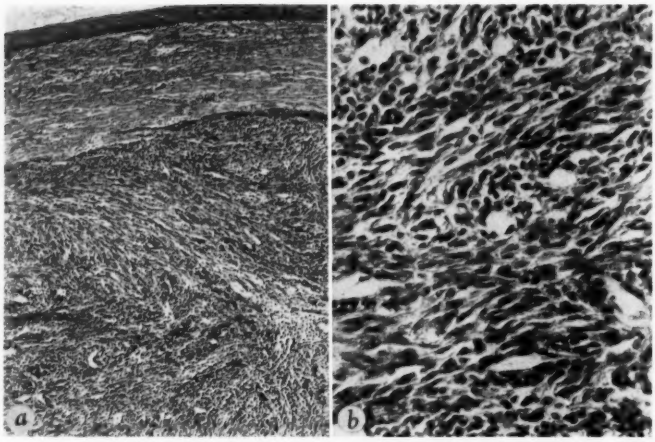


Fig. 5.—Painful leiomyosarcoma of right thigh of 1 year's duration in a 32-year-old woman. (*a*) General pattern; hematoxylin and eosin; reduced 25% from mag. ×70. (*b*) Note disorganization and immaturity of cells; hematoxylin and eosin; reduced 25% from mag. ×340.

case reported by Levack and Dick. This tissue was studied by us and by all our colleagues in surgical pathology; all of us agreed independently that the histopathologic picture presented by this tissue probably would be interpreted in this country as that of rhabdomyosarcoma rather than leiomyosarcoma. This comment is made not in the spirit of criticism but merely to emphasize the potential confusion in comparing diagnoses, which perforce will vary somewhat as interpretation varies throughout the world.

Pathologic Aspects.—Figure 5 illustrates the spindle-cell tumor found on pathologic examination. It was a small localized tumor composed of cells whose cytoplasm contained myofibrils. A number of mitotic figures were present, and it was on this criterion, as well as on the clinical evidence of malignancy, that the diagnosis was made.

Diagnosis

Once the physician becomes familiar with the variations in cutaneous myomas and realizes that painless as well as painful lesions exist, then a relatively high percentage of correct diagnoses can be made clinically. This was not true in our series, in which leiomyoma was diagnosed 9 times in 33 examinations. Other diagnoses were nevus once, sarcoid twice, xanthoma once, glomus tumor twice, neurofibroma twice, lymphocytoma once, syringoma twice, and cysts twice. The diagnosis of cyst is made most frequently with regard to nodular (dartoic) myoma. In the group of angiomyomas, which are usually solitary lesions, distinction from a painful glomus tumor or neurofibroma may be difficult clinically.

The uniform microscopic pattern in practically all leiomyomas of the skin permits one to make the histopathologic diagnosis from sections stained with hematoxylin and eosin in most instances, although special stains for connective tissue are useful. The true glomus tumor arising in connection with the glomus body has a definite pattern. neurofibroma has the typical whorling arrangement of the fibers. The other conditions mentioned under clinical differentiation present an entirely different histopathologic picture from that of leiomyoma or angiomyoma. The latter tumor may exhibit a predominance of fibrous and angiomatous tissue, or even lymphangiomatous involvement, and so one hears reference to fibromyoma or lymphangiomyoma or a combination of these terms. Some observers have mentioned the association of leiomyoma with other forms of nevi; this phenomenon was not present in any of our cases, nor was there any evidence of increase in nerve fibrils. The distinction between leiomyosarcoma, rhabdomyosarcoma, and hemangiopericytoma may require the use of special stains.

Treatment

These tumors may be allowed to remain in situ as long as they are asymptomatic. When treatment is desirable, surgical excision of the lesion or lesions is the method of choice. New lesions may occur subsequently adjacent to the region of excision of the smaller lesions of leiomyoma cutis. In many instances, excision must be followed by skin grafting because the area of involvement is so large. Ormsby suggested many years ago that they sometimes can be removed successfully by electrolysis, application of carbon dioxide snow, or fulguration. Radiotherapy apparently has no effect on the lesions or the sensations that they produce.

Summary and Conclusions

A study has been made of 33 cases of smooth-muscle tumors of the skin encountered at the Mayo Clinic. This group included 23 cases of leiomyoma cutis, 8 cases of angiomyoma, 1 case of nodular (dartoic) myoma, and 1 case of leiomyosarcoma.

Cutaneous leiomyomas only become painful when they are large enough to invade and extend around the bundles or trunks of cutaneous nerves in the deeper part of the cutis and the subcutaneous tissue. Special stains did not reveal any increase in nerve fibrils or nerve trunks. Special histochemical stains proved to be of little value in differentiating myomatous tissue.

All eight angiomyomas occurred as solitary lesions, and all were in women. The age of onset was much later in this group than in leiomyomas, which sometimes begin at birth or shortly thereafter.

Dartoic myoma is an uncommon lesion seen primarily by the surgeon because it begins in the subcutaneous tissue and calls for surgical removal.

One case of cutaneous leiomyosarcoma is reported in which recurrence was absent 21 years after surgical excision.

Mayo Clinic.

REFERENCES

1. Ormsby, O. S.: Leiomyoma Cutis, Arch. Dermat. & Syph. 11:466-480 (April) 1925.

2. Besnier, E.: Les dermatomyomes (fibromyomes, liomyomes, ou myomes cutanes), Ann. dermat. et syph. 1:25-43, 1880.

3. Kaposi, M.: Lecons sur les maladies de la peau, translated by E. Besnier and A. Doyon, Paris, G. Masson, 1881, Vol. 2, p. 346.

4. Dietel, F., in J. Jadassohn: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Springer-Verlag, 1932, Vol. 12.

5. Stout, A. P.: Solitary Cutaneous and Subcutaneous Leiomyoma, Am. J. Cancer 29:435-469 (March) 1937.

6. Stout, A. P.: Sarcomas of Soft Parts, J. Missouri M. A. 44:329-334 (May) 1947.

7. Stout, A. P.: Tumors of the Soft Tissues, in Atlas of Tumor Pathology, National Research Council, Armed Forces Institute of Pathology, 1953, Section 11, Fascicle 5, p. 38.

8. Jansen, L. H.: Leiomyomata cutis, Acta dermat.-venereol. 32:40-50, 1952.

9. Saunders, T. S., and Fitzpatrick, T. B.: Cutaneous Leiomyoma: Classification and Report of Solitary Angioleiomyoma, A. M. A. Arch. Dermat. 74:389-392 (Oct.) 1956.

10. Vilanova, X., and Grau Barbera, L.: Contribucion al conocimiento de los tumores glomicos: Forma angioleiomuscular (2° caso), Acta dermosif. 35:568-571 (March) 1944.

11. Abulafia, J., and Grinspan, D.: Leiomiomas de la piel, con especial referencia a las formas solitarias; Ensayo de classificación anátomoclinica e histogenetica, Arch. argent. dermat. 6:1-46 (March) 1956.

12. Nödl, F.: Multiple Leiomyome der Haut, ein neurocutanes Syndrom, Hautarzt 4:365-371 (Aug.) 1953.

13. Grzybowski, M.: Contribution à l'étude de l'histologie des myomes cutanés, Ann. dermat. et syph. 4:852-860 (Sept.) 1933.

14. Radermecker, J., and van Bogaert, L.: Sur la leiomyomatose douloureuse à disposition systematisée naévique (Contribution à l'étude des dysplasies mésodermiques congénitales), Dermatologica 83:201-214, 1941.

15. Sonck, C. E.: Myomatosis Cutis Miliaris: Report of a Case, Acta dermat.-venereol. 31:297-303, 1951.

16. Levack, J., and Dick, A.: Cutaneous Leiomyosarcoma with Lymphatic Spread: A Report of 2 Cases, Glasgow M. J. 36:337-342 (Oct.) 1955.

17. Ackerman, L. V., and Stout, A. P.: Leiomyosarcoma of Arm, J. Missouri M. A. 44:592-593 (Aug.) 1947.

18. Dubuisson, M.: Muscular Contraction, edited by W. Bladergroen, Springfield, Ill., Charles C Thomas, Publisher, 1954.

19. Ashmarin, I. P.: Investigation on the Properties of Contractile Muscle Proteins by New Methods, Chem. Abstr. 45:9101, 1951.

20. Barrnett, R. J., and Seligman, A. M.: Histochemical Demonstration of Protein-Bound Sulfhydryl Groups, Science 116:323-327 (Sept. 26) 1952.

21. Fishman, W. H., and Baker, J. R.: Cellular Localization of β-Glucuronidase in Rat Tissues, J. Histochem. 4:570-587 (Nov.) 1956.

22. Winkelmann, R. K., and Schmit, R. W.: A Simple Silver Method for Nerve Axoplasm, Proc. Staff Meet. Mayo Clin. 32:217-222 (May 1) 1957.

23. Winkelmann, R. K., and Schmit, R. W.: Factors Related to the Staining of Nerve Axoplasm with Concentrated Silver Solutions, Proc. Staff Meet. Mayo Clin. 32:222-226 (May 1) 1957.

ABSTRACT OF DISCUSSION

DR. HERMANN PINKUS, Monroe, Mich.: It is a very meritorious undertaking that Dr. Montgomery has discussed the smooth-muscle tumors of the skin for this Association after a lapse of more than 30 years, that is, since Dr. Ormsby presented a review of all cases published up to 1924. Now, Dr. Montgomery and Dr. Winkelmann have analyzed the rather extensive material of the Mayo Clinic and have applied the newer histolgic and histochemical techniques to these tumors. The outstanding result of their study is the demonstration that pain, which is so prominently mentioned in textbooks as a suggestive clinical symptom, really is a late sign and depends entirely on compression of nerve trunks by the tumor mass.

To gain a better basis for discussion, I reviewed my own material and found 24 cases of smooth-muscle tumors, that is, roughly, 1 case for each 1000 accessions. These were as follows: Leiomyoma cutis—16 cases (8 males and 8 females), with 15 benign and 1 malignant; angiomyoma—3 cases (2 males and 1 female), with 2 benign and 1 malignant; atypical tumors—5 cases (1 male and 4 females), with 1 deep muscle plate, 2 combined with adnexal nevus, and 2 combined with blue nevus. There were 16 leiomyomas, evidently related to arrector muscles. One of these was considered a malignant lesion and, actually, was very similar to Dr. Montgomery's illustration of leiomyosarcoma. There were only three angiomyomas, and one of these was a highly malignant tumor which apparently had originated in the smooth muscle of an artery.

Then, there were also five lesions which did not fit into either group. One of these was a thin plate of smooth muscle, consisting of bundles running at almost a 90-degree angle to each other and occupying a position at the dermosubcutaneous border. This lesion suggested dartoic origin but was a single plaque on the left shoulder of a 9-year-old girl and was of only two months' duration. The clinical diagnosis had been granuloma annulare in this case. The four other lesions seemed to be associated with nevoid disturbances of the skin, two with adnexal hamartomas of the nevus sebaceus type, and two with blue nevi.

Surprisingly, pain was not mentioned by the submitting dermatologists except in one case of angiomyoma and in one case of organoid adnexal nevus. Conversely, pruritus was mentioned four times. Clinically, the diagnosis of leiomyoma was made or suspected in only 4 of the 24 cases. This material supports Dr. Montgomery's conclusion that pain is not a very valuable symptom in the clinical diagnosis of leiomyoma. Moreover, pain is a not uncommon feature in deep-seated and fairly large dermatofibromas and histiocytomas.

I should now like to bring up one point which Dr. Montgomery mentioned and which, I think, is deserving of emphasis. How does one really identify smooth-muscle fiber in a histologic section? There is no problem, of course, in those lesions that consist of mature muscle bundles in characteristic arrangement, but is there a stain that identifies a single and morphologically atypical fiber? When the Van Gieson mixture stains fibrous tissue red and smooth muscle yellow, that is a general difference between staining of collagen and cytoplasm. Cytoplasm of fibroblasts in fibromas also stains yellow, and some unquestioned leiomyomas contain so much interstitial collagen that they look very red in Van Gieson stains. Other trichrome stains of the Masson and Mallory type are apparently of no greater usefulness, as Dr. Montgomery points out in his manuscript.

The authors have also used various histochemical procedures but apparently did not find these very helpful, either. I should like to ask Dr. Montgomery if he used Mallory's phosphotungstic acid hematoxylin, which demonstrates normal muscle, including even myoepithelial cells of sweat glands, very well. Another possibility, which was recently mentioned by Bandmann and Spier, is the plasmal reaction of Feulgen and Voit. This reaction is said to be strongly positive in normal smooth muscle but negative in fibroblasts. Unfortunately, it requires fresh tissue, which so often is not available.

One feature that has seemed helpful to me is the presence and direction of elastic fibers. Elastic fibers are closely associated with normal arrector muscle as elastic tendons at both ends and as fine fibrils between and around muscle cells. Undoubtedly, elastic fibers are not infrequently absent or reduced in leiomyomas, but, in my material, they were definitely increased in 6 out of 13 benign tumors of the arrector type, and, even if reduced in number, they often followed the direction of

the bundles—a feature that is not present in histiocytomas and fibromas. This parallelism of elastic and muscle fibers was seen in 10 of the 13 tumors.

In conclusion, I should like to congratulate Dr. Montgomery and Dr. Winkelmann on a fine piece of work.

DR. WALTER R. NICKEL, San Diego, Calif.: Dr. Montgomery mentioned a single report that he had read of a lesion referred to as nevoid leiomyoma. I can report on another case.

About three months ago, I saw a 3-week-old child. The mother stated that when she bathed the child, or when the skin was irritated, there was an area on the right lateral chest wall that would become much more red and slightly elevated. I thought that I had an unusual case of urticaria pigmentosa and proceeded to stroke the area of skin on the lateral chest wall. It immediately rose up, maybe an eighth of an inch above the surrounding skin, and became a little firmer. The response was rapid for the urtication of urticaria pigmentosa. It was not true urtication but was a rising up or elevation of the skin.

I performed a biopsy on the lesion, and, to my surprise, it was reported as "leiomyoma." Special stains confirmed the diagnosis. I presented the lesion to our local dermatological society, and no one in our area had ever seen one previously. Rather than the term "nevoid leiomyoma," I was thinking that a better name for this kind of case would be a hamartoma.

DR. FRANCESO RONCHESE, Providence, R. I.: In regard to pain, I have followed for the last 10 years a case of leiomyomata on a young woman's lower leg, having the same clinical appearance as the one in Dr. Montgomery's case in which the pain was so severe and the usual therapy was so ineffective that she submitted to a chordotomy. The procedure reduced the pain only in part. Three years later the patient developed inveterata type of psoriasis and, besides itching, still has pain.

DR. HAMILTON MONTGOMERY, Rochester, Minn. Time did not permit reference to the case of leiomyoma reported by our President, D. Finnerud, or the one reported recently by Tom Fitzpatrick and Saunders. Dr. Winkelmann and I went over probably some 150 articles, many of which simply represented single case reports.

Now, as far as the Mallory phosphotungstic acid stain goes, we have used that. We are not familiar with the plasmal-cell stain that Dr. Pinkus mentioned.

As far as the elastic fibers are concerned, all of the 33 cases were routinely stained with elastin H or Weigert stains or modifications thereof, and we could come to no definite conclusions about the increase or decrease in elastic fibers. We did find that the reticulum stained very clearly, as I showed on the screen, and that this was much more valuable than other stains. Dr. Winkelmann says he believes he can pick out 90% of the cases just by looking at a hematoxylin and eosin stain and differentiate them from neurofibromatosis or from fibromas or dermatofibromas, and so forth.

If we omit the dartoic type and the solitary deep type, which apparently occur only in women and usually in the later decades of life, the ordinary leiomyoma cutis often begins early in childhood and can be associated with other nevoid disturbances. There are a number of cases in the literature described under the term of angioleiomyoma and also fibroleiomyoma, and, in a sense, they are all hamartomas. They are benign and should not be confused with malignant rhabdomyosarcoma or liposarcomas, both of which have giant cells and are very actively growing.

It is interesting to note that my former teacher, Oliver S. Ormsby, presented a paper on leiomyoma before the American Dermatological Association in Minneapolis, in 1924, and that, despite newer histochemical methods, we have not learned much more since then.

Granuloma Faciale

CAPT. WAINE C. JOHNSON (MC); COL. ROBERT S. HIGDON (MC), U. S. Army, and ELSON B. HELWIG, M.D., Washington, D. C.

Granuloma faciale is a dermatosis characterized clinically by elevated, usually asymptomatic, reddish-brown plaques on the face. The term granuloma faciale was first used by Pinkus,[1] to define the lesions in a case he reported with Cobane and Straith.[2] Formerly this disorder had been termed eosinophilic granuloma of the skin.

A study of 15 examples of granuloma faciale has been undertaken at the Armed Forces Institute of Pathology for the purpose of determining its natural history and relation to eosinophilic granulomas and of exploring its histogenesis.

Historical Review

Eosinophilic Granuloma of the Skin.—The term "eosinophilic granuloma of the skin" was first used in 1937, by Nanta and Gadrat,[3] in reporting a patient with ulcerating lesions of the mouth and anus associated with tuberculosis. They also reviewed and included in this category a case reported by Freund[4] and another by Pautrier and associates.[5] Weidman[6] classified the lesion of Nanta and Gadrat's patient as tuberculosis cutis orificialis, of Freund's patient as atypical mycosis fungoides, and of Pautrier's patient as not diagnostic. In the French literature at this time the syphiloid of cats[7,8] was discussed and considered to be related to eosinophilic granuloma of the skin. Other cases reported as eosinophilic granuloma of the skin[9-16] have been reviewed by Buley,[17] Weidman,[6] Lewis and Cormia,[18] and Lever.[19] Weidman[6] recognized that the cases reported as eosinophilic granuloma of the skin were actually a heterogeneous group, related only by the presence of tissue eosinophilia. He divided them into two major groups: idiopathic (leukotic) and symptomatic (inflammatory). The idiopathic group included leukemia, mycosis fungoides, Hodgkin's disease, and lymphosarcoma; the symptomatic group, specific infectious diseases, toxic reactions, ids, and erythema elevatum diutinum.

Eosinophilic Granuloma of Bone.—Lichtenstein and Jaffe[20] (1940) introduced the term eosinophilic granuloma of bone to designate a disease which previously had been reported under other titles.[21-24] Farber and Green[25,26] suggested that it was a variant of Letterer-Siwe and Hand-Schüller-Christian diseases. Of this disease group referred to as the histiocytoses or reticulohistiocytoses, Letterer-Siwe is the severest and occurs chiefly in infancy; Hand-Schüller-Christian disease is less severe, and eosinophilic granuloma of bone is the mildest, both being seen principally in children but also in young adults. Several examples of eosinophilic granuloma of bone with skin involvement have been reported.[27-31]

Granuloma Faciale.—The lesions of the patient reported by Pasini[12] (1940) were limited to the face but were considered by Weidman[6] to be manifestations of aleukemic reticuloendotheliosis. The case reported by Wigley[32] (1945) appears to be the first definite example of granuloma faciale. Early cases reported or presented at meetings include those of Buley[17] (1946), Lever[19] (1947), and Hand[33] (1947), one each;

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Armed Forces Institute of Pathology. Senior Resident, Dermatology Service, Walter Reed Army Hospital (present address: Chief, Dermatology Service, Ryukyus Army Hospital, APO 331, San Francisco) (Capt. Johnson); Chief, Dermatology Service, Walter Reed Army Hospital, Washington, D. C. (Col. Higdon); Chief, Skin & Gastro-Intestinal Section, Armed Forces Institute of Pathology (Dr. Helwig).

Lever, Lane, Downing, and Spangler [34] (1948), three cases; Cooper [35] (1948), Oliver and associates [36] (1949), Cobane, Straith, and Pinkus [2] (1950), and Boersma [37] (1950), one each, and Lever and Leeper [31] (1950), Peck, Palitz, and Reiner [38] (1952), two each. In 1952 Pinkus [39] reported three new cases and reviewed the world literature. He concluded that a total of 29 cases, including the ones in his report, had been recognized at that time. Additional examples have been recognized in several countries since 1952.

Material and Methods

Of the 15 cases in our series at Armed Forces Institute of Pathology, 1 has been reported previously by Cobane, Straith, and Pinkus [2] and another presented by Weidman [40] at the American Academy of Dermatology and Syphilology exhibit and panel discussion on histopathology. Special staining procedures were performed in 10 cases. The methods employed included Hart's elastic, Snook's reticulum, Gram (Brown and Brenn modification), Gomori's methenamine silver nitrate for fungus, Ziehl-Neelsen and Fite for acid-fast bacteria, Perl's iron, Fontana's for argentaffin granules, toluidine blue, polychrome methylene blue, Giemsa, periodic acid-Schiff (PAS) reaction with and without diastase digestion, Van Gieson's, Weigert's Gram, crystal violet, phosphotungstic acid hematoxylin with and without trypsin digestion for three hours, and oil red O. Sections were examined under polarized light and after microincineration.

Follow-up data and answers to a special questionnaire were received in 13 cases.*

Clinical Course

The clinical appearance of granuloma faciale, in the 15 patients we have studied, was that of a plaque or nodule in 12 and of macules in 3. The lesions were soft and usually brown, red, or purple and varied from a few millimeters to 8 cm. in diameter. In two patients the center of the lesion was depressed (Fig. 1). Occasionally the follicular openings were dilated. The lesions never ulcerated or drained, except secondarily to surgical procedures. A few patients noticed moderate variations in the substance, color, and conspicuousness of the lesions. In 6 of the 15 patients the lesion was single; the greatest number seen in any patient was 9. All were limited to the face. They were distributed in decreasing order of frequency on the sides of the nose, preauricular areas, cheeks, forehead, tip of nose, and helix of the ear. Five of the patients were asymptomatic, while the rest noticed varying degrees of itching, stinging, or tenderness. The lesions of four patients were aggravated by sunlight and those of two, by heat.

Fig. 1.—A reddish-brown plaque with a depressed center on the forehead. Lesions with depressed centers were seen in only 2 of the 15 patients. AFIP Neg. 58-5221.

Three patients had sustained an injury or laceration in the area of involvement prior to onset of the granuloma, but a definite relationship between the two could not be established. Six of the patients had a history of one or more of the following "al-

TABLE 1.—*Anatomical Sites of Lesions*

Site	Patients, No.
Sides of nose	8
Preauricular areas	6
Cheeks	6
Forehead	4
Tip of nose	2
Helix of ear	1

* Drs. J. L. Arbogast, Herman Beerman, L. M. Mason, Herman Pinkus, E. M. Satulsky, Claire Straith, and Herbert F. Williams obtained and granted permission for use of additional clinical data and follow-up information.

TABLE 2.—*Age Distribution of Patients at Onset*

Age	No.
25-29	1
30-39	5
40-49	3
50-59	4
60-65	2
Total	15

lergic diseases": hay fever, asthma, hives, sinusitis, and drug allergy. Three had acne rosacea and one of these observed aggravation of the granuloma faciale concomitant with a flare-up of the rosacea. Four patients had infected teeth; two had a heart murmur following streptococcal sore throat. None of the patients had relatives with granuloma faciale. On specific questioning all of the patients denied having had any disease of bone.

All except 1 of our 15 patients were men. The age at onset of the disease varied from 25 to 65 years. All patients were white; most had fair skin and blonde to brown hair. The disease did not appear to be regional; the patients had lived in all parts of the United States before onset of the lesions.

The initial clinical differential diagnoses in our series, in decreasing order of frequency, were lupus erythematosus, sarcoidosis, eosinophilic granuloma, lymphoma, leukemia, erythema elevatum diutinum, fixed drug eruption, leprosy, granuloma, and Bowen's disease.

A complete blood cell count in each of seven patients was normal, except for an eosinophilia of 7% in one patient. The results of other routine laboratory examinations were normal, and roentgenologic bone survey performed on two patients was negative.

The patients in our series were treated by the following methods: surgical excision, x-ray, electrodesiccation, freezing with solid carbon dioxide (Dry Ice), gold injections, bismuth orally and intramuscularly, testosterone, cortisone, chloroquine, *p*-aminobenzoic acid, calciferol (Drisdol), isoniazid, iodides, potassium arsenite (Fowler's solution) orally, dermabrasion, penicillin, and sun-protective creams.

The results of treatment, except when complete removal or destruction of the lesion was accomplished, were uniformly poor. In a few patients, surgical excision cured an individual lesion permanently, while in others recurrence arose in the scar. Response to x-ray therapy was poor. Drug therapy, on the whole, was ineffectual. In one case temporary flattening of a lesion followed treatment with chloroquine. Applications of solid carbon dioxide produced definite improvement in several instances. None of the lesions disappeared without treatment, although only minimal residual pigmentation and atrophy were seen on examination of one patient 13 years after onset.

The period of follow-up ranged from 1 to 24 years after onset of the disease, and the average was 8.9 years. Two patients were completely clear of lesions at follow-up one and five years, respectively, after excision of the lesions. The other patients still had one or more persistent lesions.

Pathologic Observations

The tissue sections from each lesion showed a cellular infiltrate in the corium separated from the epidermis by a narrow relatively uninvolved (grenz) zone (Fig. 2). The epidermis was unchanged except for flattening of the rete ridges. A narrow zone of normal connective tissue separated the epidermal appendages from the cellular infiltrate, which was usually located in the upper and middle corium but occasionally involved the entire corium and the upper part of the subcutaneous tissue. In the more extensive lesions the infiltrate was diffuse, although more concentrated perivascularly (Fig. 3). In smaller lesions the infiltrate was limited to perivascular sites. In a few lesions there was appreciable fibrosis (Fig. 4).

The cellular infiltrate was of mixed cell type. Leukocytes, either eosinophilic or neutrophilic, were present in all lesions.

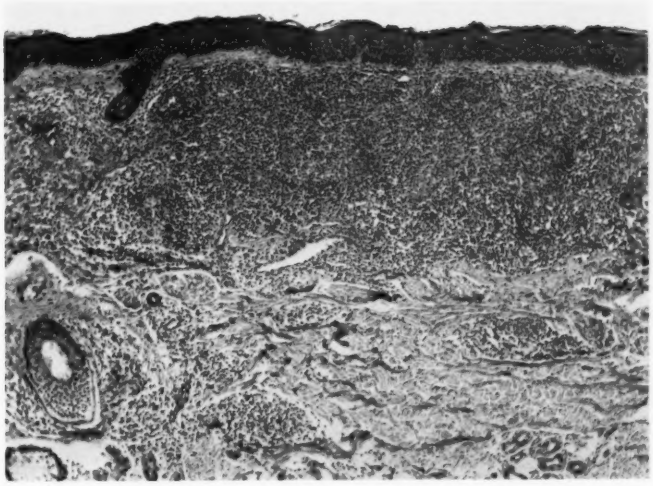

Fig. 2.—The epidermis is normal except for flattening of the rete ridges. There is a cellular infiltrate in the upper corium separated from the epidermis by a narrow (grenz) zone of normal connective tissue. Hematoxylin and eosin; (AFIP Acc. 518482) AFIP Neg. 58-7661; reduced approximately 10% from mag. × 55.

Eosinophilic leukocytes usually predominated, but in two instances the neutrophilic cells predominated with only an occasional eosinophil (Fig. 5). Frequently, mononuclear eosinophils were also present. Other cell types represented included histiocytes, lymphocytes, mast cells, plasma cells, and fibrocytes.

The changes in blood vessels were of particular interest because the reaction was centered about them. In the upper corium the capillaries and small venules were dilated, but often neither the endothelium nor the wall was appreciably thickened. Around some of these vessels the nuclei of the inflammatory cells were fragmented and an acidophilic-staining material was laid down in a trabecular pattern. This material usually appeared to be outside the vessel wall and not to involve the wall directly. It was prominent in only a few specimens and was not a constant feature. Extravasation of red blood cells into the perivascular areas with deposition of hemosiderin was fairly common.

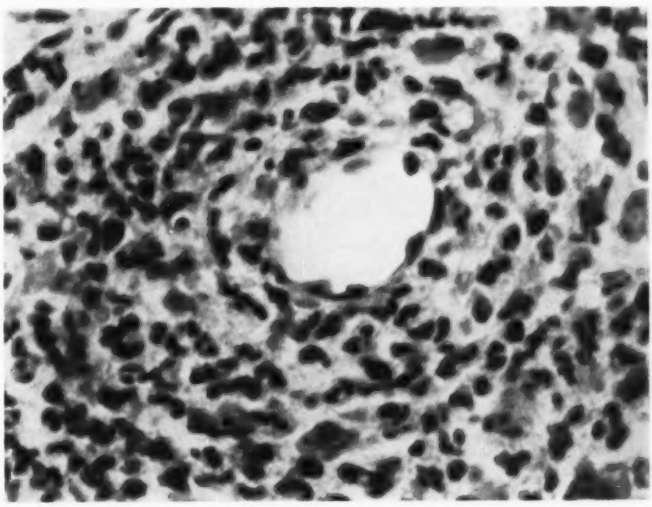

Fig. 3.—A dense cellular infiltrate concentrated around a capillary is composed of a mixture of mature inflammatory cells with eosinophils, leukocytes predominating. Hematoxylin and eosin; (AFIP Acc. 260096) AFIP Neg. 52-1219; reduced approximately 15% from mag. × 1000.

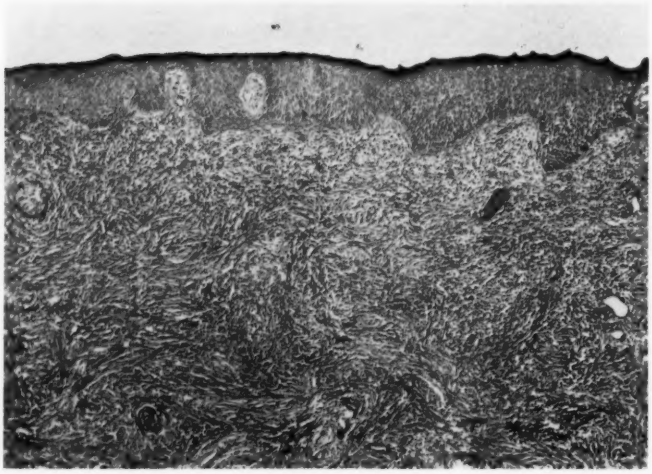

Fig. 4.—Fibrosis of the connective tissue in the upper corium, an outstanding feature in this lesion, pathologically represents a late stage of granuloma faciale. Hematoxylin and eosin; (AFIP Acc. 753696) AFIP Neg. 58-5896; reduced approximately 10% from mag. × 50.

Almost complete destruction of elastic fibers in the areas of cellular infiltration was demonstrated by Hart's elastic stain, thus emphasizing the narrow normal (grenz) zone of connective tissue immediately beneath the epidermis. The Snook reticulum stain revealed an increased number of fine reticulum fibers in the infiltrate. Examination of sections stained with Gram (Brown and Brenn modification), Gomori's methenamine silver, Ziehl-Neelsen, Fite, and Giemsa stains did not reveal micro-organisms. The Perl iron reaction was moderately positive perivascularly. This correlates with the reddish iron ash seen in these areas on microincineration. The Fontana stain demonstrated a normal amount of melanin in the epidermis above the infiltrate but only a small amount in the cellular infiltrate. Toluidine blue, methylene blue, and Giemsa stains were employed to study mast cells, which were seen throughout the infiltrate but were more numerous around the blood vessels and epidermal appendages. In these areas 10

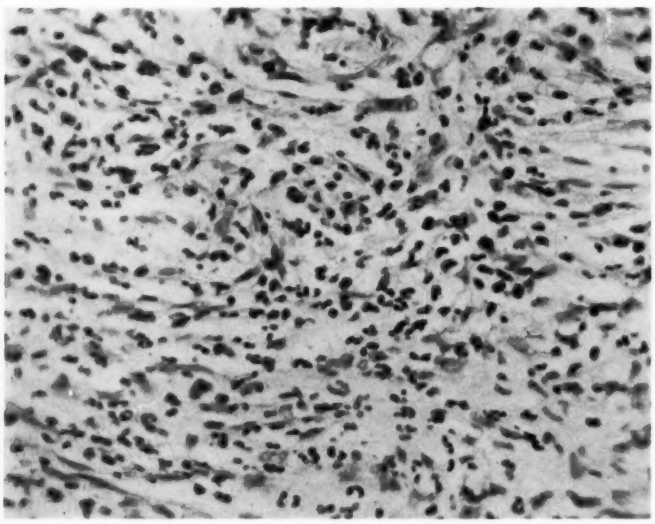

Fig. 5.—A higher power of the lesion seen in Figure 4 reveals numerous neutrophilic leukocytes and a few eosinophilic ones. In most lesions eosinophils predominate. Hematoxylin and eosin; (AFIP Acc. 753696) AFIP Neg. 57-13486; reduced approximately 15% from mag. × 440.

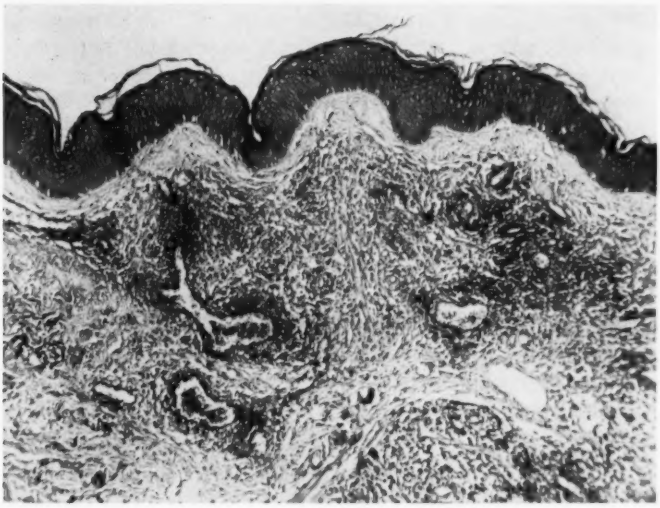

Fig. 6.—The perivascular material seen in a few lesions is similar, if not identical, morphologically and histochemically, to the "toxic hyalin" or erythema elevatum diutinum and to "fibrinoid" of the so-called collagen diseases. Phosphotungstic acid hematoxylin; (AFIP Acc. 640362) AFIP Neg. 58-7664; reduced approximately 15% from mag. × 70.

mast cells per high-power field was not uncommon. The acidophilic material seen perivascularly in some cases was moderately positive with the PAS reaction and was not digested with diastase. This material was yellow in sections stained by Van Gieson's method, purple with crystal violet, and blue to blue-black with phosphotungstic acid hematoxylin (Figs. 6 and 7) and resisted digestion with trypsin. Weigert's Gram stain for fibrin was negative. Examination of paraffin tissue sections under polarized light did not reveal doubly refractile foreign material. Oil red O stain on relatively early lesions, in two cases, did not reveal an appreciable amount of fat in the involved areas.

Comment

Clinical Aspects.—The sex ratio of 14 men to 1 woman is not representative of the general population, since most of the material at the Armed Forces Institute of Pathology is obtained from the predomi-

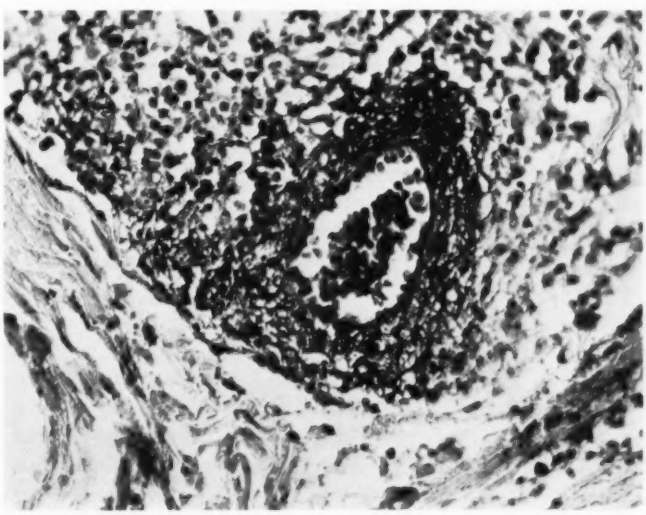

Fig. 7.—On higher magnification the phosphotungstic acid-hematoxylin-positive material is seen primarily around and outside of the blood vessel wall. Phosphotungstic acid hematoxylin; (AFIP Acc. 640362) AFIP Neg. 58-7666; reduced approximately 15% from mag. × 325.

nantly male population of the Armed Forces and Veterans' Administration. Probably a ratio of about three men to one woman, as obtained from review of previously reported cases, is more representative. It seems significant that none of our patients were Negroes and that we have not found a report of the disease in Negroes. Ten of our fifteen patients noticed varying degrees of itching, burning, stinging, or tenderness, which is in contrast to the general impression that the lesions are asymptomatic. Although the lesions tended to persist indefinitely, at times their color and substance varied. Depression of the center of the lesions seen in two patients is a morphological variation previously unreported. The association with "allergic diseases" and foci of infection will be considered in connection with pathogenesis.

The results of laboratory examinations were normal in our series, except for an eosinophilia of 7% in one patient. Moderate eosinophilia has been reported in a few instances, and its presence may depend on the stage of the process at the time of examination.

The results of treatment in this series are similar to those in cases previously reported. It appears that wide surgical excision is the treatment of choice if this approach is feasible. With multiple or widespread lesions, freezing with solid carbon dioxide may effect improvement. If the appearance of the lesion is not objectionable cosmetically, there is some question as to whether treatment is required, because wide excision of lesions has not always prevented occurrence of new lesions in other sites at a later date. From an investigative standpoint, it might be worth while to treat additional patients with antimalarial drugs in conjunction with sun-screening agents, since photosensitization appears to be a possible factor in some patients.

Relation to Other Eosinophilic Granulomas.—Our data confirm the observations of earlier investigators [1,31,41] that granuloma faciale is entirely unrelated to eosinophilic granuloma of bone. All patients in our series and those reported by others have been adults. On specific questioning, none of the patients in our group gave a history of bone disorders or other symptoms related to the histocytosis group. A roentgenographic skeletal survey in two patients and a partial survey in others revealed no abnormalities. The results of roentgenographic survey performed on at least six patients previously reported have been normal. There is no evidence to suggest a direct relation of granuloma faciale to the heterogeneous group previously reported as eosinophilic granuloma.

Differential Diagnosis.—Clinically, granuloma faciale must be distinguished from all those conditions which may exhibit elevated or macular reddish-brown single or multiple lesions on the face. Clinically, lupus erythematosus, polymorphic light erruption, benign lymphocytic infiltration, sarcoidosis, lymphoma, mycosis fungoides, granuloma annulare, urticaria pigmentosa, fixed drug eruption, erythema elevatum diutinum, xanthoma, xanthogranuloma, and Bowen's disease may simulate granuloma faciale. All of them have certain characteristic clinical differences from granuloma faciale, but if they are atypical or in early stages the diagnosis may be confused. A biopsy correlated with the clinical picture is required for definitive diagnosis.

Histopathologically, granuloma faciale must be differentiated from all those conditions in which the outstanding feature is a cellular infiltrate in the upper corium. These include lupus erythematosus, polymorphic light eruption, benign lymphocytic infiltration (lymphocytoma), lichen planus, drug eruption, secondary syphilis, lymphoma, mycosis fungoides, Hodgkin's disease, insect-bite granuloma, the histiocytosis group, erythema elevatum diutinum, and urticaria pigmentosa. Two features that invariably are present in granuloma faciale provide the most useful diagnostic criteria: (*a*) The cellular infiltrate in the upper corium is separated from the epidermis by

a narrow (grenz) zone of normal tissue; (*b*) it is composed of a mixture of mature cells, predominantly leukocytes—eosinophilic, neutrophilic, or both—centered perivascularly. Two other criteria are not constant but are significant when present: (*c*) fragmentation of nuclei of polymorphonuclear leukocytes and acidophilic material around the blood vessels; (*d*) fibrosis of connective tissue, which probably represents a relatively late stage. The diagnostic significance of the grenz zone and the early leukocytic and later fibrotic stages have been stressed by Lever.[41]

Some of the conditions from which granuloma faciale must be differentiated deserve individual consideration because of their serious nature or close resemblance to granuloma faciale. Mycosis fungoides has an infiltrate of mixed cell type that may include eosinophils. However, the large atypical reticulum cells (mycosis cells), monocytes, and histiocytes contrast with the predominantly polymorphonuclear cells seen perivascularly in granuloma faciale. In addition, the epidermis in mycosis fungoides is usually acanthotic and may include microabscesses containing mononuclear cells (Pautrier). Specific infiltrations of Hodgkin's disease in the skin are rare but when they occur are characterized by Dorothy-Reed-Sternberg giant cells. Eosinophilic granuloma of bone and the lesions of Letterer-Siwe and Hand-Schüller-Christian diseases are primarily histiocytic cell infiltrates and can be easily distinguished.[1,30,41] Urticaria pigmentosa may be more difficult to differentiate because the infiltrates contain eosinophilic and some neutrophilic leukocytes. In our material such an example was noted and the correct diagnosis was made after stains for mast cells were obtained. Benign lymphocytic infiltration and lupus erythematosus have a mixture of inflammatory cells but lack the numerous eosinophilic and neutrophilic leukocytes seen in granuloma faciale. Drug eruptions may appear in a variety of morphologic patterns, including a perivascular infiltrate, but an abundance of leukocytes would be unusual. In polymorphic light eruption the perivascular infiltrate may be chiefly of leukocytes, but usually it is predominantly of lymphocytes. The similarity to erythema elevatum diutinum has been recognized since the early descriptions, and Weidman [6] used the term "erythema elevatum diutinum type of eosinophilic granuloma of the skin." Sections of the lesions of erythema elevatum diutinum, as determined in sections from areas other than the face, lack the flattened epidermis and grenz zone. Acidophilic material, when present in our cases, appeared to be principally around the blood vessels rather than in the walls, as described in erythema elevatum diutinum. This apparent difference may be related to the stage or intensity of the reaction and not represent a basically different process.

Pathogenesis and Etiology.—Previous reports on granuloma faciale have been concerned primarily with defining the clinical and pathologic features and separating the lesion from the other eosinophilic granulomas. Less attention has been given to pathogenesis and etiology. First, let us consider the closely related reaction seen in erythema elevatum diutinum. Clinically, it is a persistent eruption consisting of elevated reddish plaques, often with clearing in the center and extension at the periphery, usually located over the joints and at sites of trauma. The pathological reaction is somewhat similar to that in granuloma faciale. Weidman [42] has pointed out the relationship of erythema elevatum diutinum to the rheumatic states and presented strong evidence to incriminate a "hypersensitivity" to streptococcal infection.

The acidophilic material around the vessels in granuloma faciale is similar, if not identical, morphologically and histochemically, to the "toxic hyalin" of erythema elevatum diutinum and to "fibrinoid" seen in the so-called collagen diseases. This material in granuloma faciale was PAS-positive and stained yellow with Van Gieson's,

purple with crystal violet, and blue with phosphotungstic acid hematoxylin stains and was not digested by trypsin. These findings are consistent with fibrinoid, as described by Altshuler and Angevine.[43] In the past it has been debated whether fibrinoid was due to inspissation of fibrin or other blood derivatives,[44] degeneration of collagen,[45] or precipitation of the ground substance.[43] Altshuler and Angevine [43] concluded that fibrinoid results from precipitation of the acid mucopolysaccharide of the ground substance and that the precipitant in some instances is probably an alkaline protein derived from the interaction of tissue with a damaging agent. Gitlin, Craig, and Janeway,[46] using fluorescein-labeled rabbit antisera against human fibrin, concluded that at least a part of fibrinoid material is fibrin. The basic changes in lesions attributed to hypersensitivity in man [47,48] and those produced experimentally in animals [49] consist of evidence of increased capillary permeability, swelling and fibrinoid necrosis of the connective tissue, and an infiltrate frequently in association with small blood vessels. The vessel wall itself may or may not be involved.[50] These changes, and particularly fibrinoid, have been produced by methods other than hypersensitivity, including simple squeezing of tissue,[51] prolonged passive hyperemia,[52] and large doses of deoxycorticosterone acetate.[53]

The pathologic reaction is not specific, but, in association with the clinical course, it suggests to us that the basic pathophysiological process is an antigen-antibody or hypersensitivity reaction. The "shock" tissues for the reaction are the small blood vessels and perivascular areas of the upper corium. This could be a reaction pattern elicited by single or multiple exciting factors which may not necessarily be the same in every case. The exciting factors remain unknown, but, on the basis of our material, foci of infection, sunlight, trauma, and drugs must be considered.

Infection.—Lack of micro-organisms on special stains, absence of suppuration, and the histopathologic pattern rule against a local cellulitis in the areas involved. However, toxins and antigenic bacterial products from a distant focus deserve attention. Of the 13 patients in our group with follow-up murmur following a streptococcal sore information, 4 had infected teeth; 2, a heart throat; 3, sinusitis; 1, septic arthritis, and 3, acne rosacea. One patient noted an exacerbation of the lesions of granuloma faciale at times when his rosacea flared up. Eight patients had one or more foci of infection at the time of or shortly before onset of the lesions of granuloma faciale.

Sunlight.—Because the lesions in our patients were always on the face, and reported elsewhere in only one case, the effect of sunlight must be evaluated. Four patients noticed aggravation of the lesions on exposure to sunlight, and one stated that his lesions became almost black when he was in the tropics in World War II. As far as we can determine, all of the patients reported have been white; most of ours had fair skin and blonde to brown hair. The lesions of one patient treated with chloroquine were temporarily flattened. Thus, there is evidence to support, but no proof, that photosensitivity plays a role.

Trauma.—Three of our patients had sustained trauma to the sites later involved by the lesions, but a definite causal relationship could not be established.

Drugs.—Although no drugs were implicated in our series, we do not believe that they can be dismissed from consideration. Drugs are known to produce a wide variety of reactions, some of them similar to that seen in granuloma faciale. For example, the pathological change in allergic sulfonamide reactions is fibrinoid necrosis with an eosinophilic cellular infiltrate.[54] Furthermore, photosensitivity is known to be an associated factor in these reactions.

Summary and Conclusions

The natural history of granuloma faciale is characterized by the onset in adults of single or multiple elevated brown, red, or

purple plaques on the face. New lesions may develop over a period of several months. Ten of our fifteen patients noticed varying degrees of itching, burning, stinging, or tenderness. Response to therapy other than wide excision is poor. The lesions in most patients tend to persist indefinitely but vary in color and substance from time to time. The general health of the patients has remained good.

Our material yielded no evidence of any relationship between granuloma faciale and eosinophilic granuloma of bone or the heterogeneous conditions once called eosinophilic granuloma.

Our observations suggest that the pathogenesis of granuloma faciale is basically an antigen-antibody or hypersensitivity reaction, the small blood vessels and perivascular tissues in the upper corium of the face being the "shock" tissues.

The exciting agents are unknown, but we regard foci of infection, photosensitivity, trauma, and drugs as possibilities.

REFERENCES

1. Pinkus, H.: Symposium on Diseases of the Skin: Granulomas with Eosinophilia ("Eosinophilic Granulomas"), M. Clin. North America 35:463 (March) 1951.

2. Cobane, J. H.; Straith, C. L., and Pinkus, H.: Facial Granulomas with Eosinophilia: Their Relation to Other Eosinophilic Granulomas of the Skin and to Reticulogranuloma, Arch. Dermat. & Syph. 61:442 (March) 1950.

3. Nanta, A., and Gadrat, J.: Sur un Granulome éosinophilique cutané, Bull, Soc. franç. dermat. et syph. 44:1470 (May) 1937.

4. Freund, E.: Su un caso di strani tumori cutanei in una tuberculosa, Dermosifilografo 5: 617 (Oct.) 1930.

5. Pautrier, L. M.; Glasser, R., and Labourgade, A.: Lésions verruqueuses, végétantes, éléphantiasiformes, du pourtour de l'orifice anal, de tout le pli fessier et du scrotum, s'accompagnant de lésions végétantes endo-rectales pouvant faire penser à une maladie de Nicolas-Favre, mais de nature indéterminée, Bull. Soc. franç. dermat. et syph. 43:896 (May) 1936.

6. Weidman, F. D.: The "Eosinophilic Granulomas" of the Skin, Arch. Dermat. & Syph. 55:155 (Feb.) 1947.

7. Henry, A., and Bory, L.: La Syphiloïde du chat, Bull. Soc. franç. dermat. et syph. 41:959 (June) 1934.

8. Henry, A., and Bory, L.: La Syphiloïde du chat (granulome éosinophilique), Bull. Soc. franç. dermat. et syph. 44:1486 (July) 1937.

9. Martinotti, L.: Contributo allo studio della eosinofilia istogena cutanea, Arch sc. méd. 46:259 (June) 1923.

10. Lefevre, P.; Coirre, and Levy-Coblentz, G.: Granulomatose cutanée à évolution fébrile avec éosinophilie sanguine à 46% san déterminations ganglionnaires, Bull. Soc. franç. dermat. et syph. 44:1604 (July) 1937.

11. Lapiere: Un Cas de granulome éosinophilique, Bull. Soc. franç. dermat. et syph. 44:1479 (July) 1937.

12. Pasini, A.: Granuloma eosinofilo (reticoloendotelios: proliferation), Gior. ital. dermat. e sif. 81:19 (Feb.) 1940.

13. Martinotti, L.: Zur Frage des eosinophilen Granuloms, Dermat. Wchnschr. 112:25 (Jan.) 1941.

14. Cerutti, P.: Il granuloma eosinofilo, Dermatologica 85:90-132, 1942.

15. Lewis, G. M.: A Case for Diagnosis (Eosinophilic Granuloma?), Arch. Dermat. & Syph. 53:375 (May) 1946.

16. Klauder, J. V., and Weidman, F. D.: A Case for Diagnosis (Eosinophilic Granuloma?), Arch. Dermat. & Syph. 53:559 (May) 1946.

17. Buley, H. M.: Eosinophil Granuloma of the Skin, J. Invest. Demat. 7:291 (Dec.) 1946.

18. Lewis, G. M., and Cornia, F. E.: Eosinophilic Granuloma: Theoretic and Practical Considerations Based on the Study of a Case, Arch. Dermat. & Syph. 55:176 (Feb.) 1947.

19. Lever, W. F.: Eosinophilic Granuloma of the Skin: Its Relation to Erythema Elevatum Diutinum and Eosinophilic Granuloma of the Bone, Report of a Case, Arch. Dermat. & Syph. 55:194 (Feb.) 1947.

20. Lichtenstein, L., and Jaffe, H. L.: Eosinophilic Granuloma of Bone, with Report of a Case, Am. J. Path. 16:595 (Sept.) 1940.

21. Finzi, O.: Mieloma con prevalenza della cellule eosinofile, circoscritto all'osso frontale in un giovane di 15 anni, Minerva med. 9:239 (Feb.) 1929.

22. Mignon, F.: Ein Granulationstumor des Stirnbeins, Fortschr. Geb. Röntgenstrahlen 42: 749 (Dec.) 1930.

23. Schairer, E.: Über eine eigenartige Erkrankung des kindlichen Schädels (Osteomyelitis mit eosinophiler Reaktion), Zentralbl. allg. Path. 71: 113 (Nov.) 1938.

24. Otani, S., and Ehrlich, J. C.: Solitary Granuloma of Bone Simulating Primary Neoplasm, Am. J. Path. 16:479 (July) 1940.

25. Farber, S.: The Nature of "Solitary or Eosinophilic Granuloma" of Bone, Am. J. Path. 17:625 (July) 1941.

26. Green, W. T., and Farber, S.: "Eosinophilic or Solitary Granuloma" of Bone, J. Bone & Joint Surg. 24:499 (July) 1942.

27. Curtis, A. C., and Cawley, E. P.: Eosinophilic Granuloma of the Bone with Cutaneous Manifestations: Report of a Case, Arch. Dermat. & Syph. 55:810 (June) 1947.

28. McCreary, J. H.: Eosinophilic Granuloma with Simultaneous Involvement of Skin and Bones, Arch. Dermat. & Syph. 58:372 (Oct.) 1948.

29. Kendrick, J. I., and Woodruff, J. B., Jr.: Eosinophilic Granuloma: Report of a Case with Both Osseous and Cutaneous Lesions, Cleveland Clin. Quart. 15:26 (Jan.) 1948.

30. Pinkus, H.; Copps, L. A., Custer, S., and Epstein, S.: Reticulogranuloma: Report of a Case of Eosinophilic Granuloma of Bone Associated with Nonlipid Reticulosis of Skin and Oral Mucosa Under the Clinical Picture of Hand-Schüller-Christian Disease, Am. J. Dis. Child. 77:503 (April) 1949.

31. Lever, W. F., and Leeper, R. W.: Eosinophilic Granuloma of the Skin, Arch. Dermat. & Syph. 62:85 (July) 1950.

32. Wigley, J. E. M.: ?Sarcoid of Boeck: ?Eosinophilic Granuloma, Brit. J. Dermat. 57:68 (March-April) 1945.

33. Hand, E. A.: A Case for Diagnosis (Eosinophilic Granuloma of Skin?), Transactions of the Detroit Dermatological Society, February, 1947.

34. Lever, W. F.; Lane, C. G.; Downing, J. G., and Spangler, A. S.: Eosinophilic Granuloma of the Skin: Report of 3 Cases, Arch. Dermat. & Syph. 58:430 (Oct.) 1948.

35. Cooper, Z. K.: Eosinophilic Granuloma of Skin: Pathologic Round Table, read before the American Academy of Dermatology and Syphiology, Chicago, December, 1948.

36. Oliver, E. A.; Webster, J. R.; Ginsberg, J. E., and Steinberg, H. S.: Eosinophilic Granulomas of the Skin, Arch. Dermat. & Syph. 60:701 (Nov.) 1949.

37. Boersma, D.: Facial Granuloma with Eosinophilia, Tr. Detroit Dermat. Soc., March, 1950.

38. Peck, S. M.; Palitz, L. L., and Reiner, E.: Facial Granuloma with Eosinophilia (Granuloma Faciale), A. M. A. Arch. Dermat. & Syph. 65:216 (Feb.) 1952.

39. Pinkus, H.: Granuloma Faciale, Dermatologica 105:85, 1952.

40. Weidman, F. O.: American Academy of Dermatology and Syphilology Exhibit and Panel Discussion on Histopathology, Chicago, Dec. 10, 1952.

41. Lever, W. F.: Histopathology of the Skin, Philadelphia, J. B. Lippincott Company, 1949.

42. Weidman, F. D., and Besancon, J. H.: Erythema Elevatum Diutinum: Rôle of Streptococci, and Relationship to Other Rheumatic Dermatoses, Arch. Dermat. & Syph. 20:593 (Nov.) 1929.

43. Altshuler, C. H., and Angevine, D. M.: Histochemical Studies on the Pathogenesis of Fibrinoid, Am. J. Path. 25:1061 (Sept.) 1949.

44. Clark, E.; Graef, I., and Chasis, H.: Thrombosis of the Aorta and Coronary Arteries, with Special Reference to the "Fibrinoid" Lesions, Arch. Path. 22:183 (Aug.) 1936.

45. Klemperer, P.; Pollack, A. D., and Baehr, G.: Pathology of Disseminated Lupus Erythematosus, Arch. Path. 32:569 (Oct.) 1941.

46. Gitlin, D.; Craig, J. M., and Janeway, J. C. A.: Studies on the Nature of Fibrinoid in the Collagen Diseases, Am. J. Path. 33:55 (Jan.-Feb.) 1957.

47. Rich, A. R.: The Role of Hypersensitivity in Periarteritis Nodosa: As Indicated by 7 Cases Developing During Serum Sickness and Sulfonamide Therapy, Bull. Johns Hopkins Hosp. 71:123 (Sept.) 1942.

48. Bergstrand, H.: Morphological Equivalents in Polyarthritis Rheumatica, Periarteritis Nodosa, Transient Eosinophilic Infiltration of the Lung and Other Allergic Syndromes, J. Path. & Bact. 58:399 (July) 1946.

49. Fox, R. A., and Jones, L. R.: Vascular Pathology in Rabbits Following Administration of Foreign Protein, Proc. Soc. Exper. Biol. & Med. 55:294 (April) 1944.

50. More, R. H.; McMillan, G. C., and Duff, G. L.: The Pathology of Sulfonamide Allergy in Man, Am. J. Path. 22:703 (July) 1946.

51. Wu, T. T.: Über Fibrinoidbildung der Haut nach unspezifischer Gewebsschädigung bei der Ratte, Arch. path. Anat. 300:373 (Aug.) 1937.

52. Henschen, F.: Über eine eigenartige, mit Thrombenbildung verbundene Reaktion des Gefässendothels, Acta med. scandinav. 65:539, 1926-1927.

53. Selye, H.: The General Adaptation Syndrome and the Diseases of Adaptation, J. Clin. Endocrinol. 6:117 (Feb.) 1946.

54. Alexander, H. L.: Reactions with Drug Therapy, Philadelphia, W. B. Saunders Company, 1954.

Fungistasis of Hydrocortisone and Certain of Its Analogues

ROBERT L. SAUVAN, M.A., and RICHARD L. SUTTON Jr., M.D., Kansas City, Mo.

Topically applied, hydrocortisone and related chemical substances are in common dermatologic use. We have observed their beneficial effects upon many patients with dermatoses clinically resembling dermatophytosis. We therefore wished to know whether hydrocortisone and certain of its analogues were fungistatic in vitro. A search of the literature disclosed no data bearing directly on this question.

Method

Organisms selected for study were common dermatophytes, Trichophyton rubrum, Trichophyton gypseum, Microsporum audouini, Microsporum canis, and Candida albicans.

With use of finely pulverized hydrocortisone tablets, which proved insoluble in water, a suspension was first made in 95% ethyl alcohol before incorporation in Sabouraud's medium. In 0.1% hydrocortisone in Sabouraud's medium so prepared, C. albicans was the only organism that grew. Control media, containing the same amount of alcohol but no hydrocortisone, were inoculated with the several organisms, and again only C. albicans grew. It appeared that the presence of alcohol rather than the presence of hydrocortisone was concerned with the failure of the other dermatophytes to grow.

Supplies were obtained of pure hydrocortisone acetate, hydrocortisone alcohol, prednisolone phosphate, and prednisolone alcohol.* Hydrocortisone acetate and hydrocortisone alcohol made a coarse suspension in water; prednisolone alcohol yielded a finely crystalline suspension, and prednisolone phosphate was soluble. Media were made containing 0.1% and 0.9% of the two hydrocortisones and 1.0% of the two prednisolones. Small segments, approximately 3 mm. square, of mycotic growth from recent subcultures of stock cultures were ground with a glass rod in 2 cc. of physiological saline. No effort was made to secure accurately quantitative concentrations of the fungus suspensions. Except with C. albicans, where 0.25 cc. was used, 0.5 cc. of each suspension was transferred to 4 cc. of saline. One-tenth cubic centimeter of these dilutions was plated on Sabouraud's medium in each case. Previous trial dilutions indicated that this procedure consistently yielded optimal growth.

Results

Results of the tests are shown in the Table. In all cases sterility controls were satisfactory. In the media containing the two hydrocortisones in 0.1% concentration, T.

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* These were supplied by Sharp and Dohme, Division of Merck & Co., Inc.

Growth of Certain Dermatophytes in Various Concentrations of Some Hydrocortisone and Prednisolone Compounds

	T. Gypseum	M. Audouini	T. Rubrum	M. Canis	C. Albicans	Sterility
Hydrocortisone acetate 0.1%	+ *	+	No growth	No growth	+	O. K.
Hydrocortisone alcohol 0.1%	+	+	No growth	No growth	+	O. K.
Control	+	+	+	No growth	+	
Hydrocortisone acetate 0.9%	+	+	+	+	+	O. K.
Hydrocortisone alcohol 0.9%	+	+	+	+	+	O. K.
Control	+	+	+	No growth	+	
Prednisolone phosphate 1.0%	+	No growth	+	+	+	O. K.
Prednisolone alcohol 1.0%	+	No growth	+	+	+	O. K.
Control	+	+	+	+	+	

* + means uninhibited growth; — means not tested.

rubrum failed to grow, although it grew in the control. M. canis grew neither on the test medium nor on the control. The other organisms grew well on both test and control media. Media containing the hydrocortisones in 0.9% concentration were inoculated with all five organisms tested. These grew; there was no fungistatic effect.

In 1.0% concentrations of the prednisolones, uninhibited growth occurred with all dermatophytes tested except M. audouini. The failure of M. audouini to grow under these conditions is unexplained. We suspect that this was not due to a fungistatic property of the compounds. Note that neither M. canis nor T. rubrum grew in the 0.1% dilutions of the hydrocortisones, but they did grow in the 0.9% dilutions. This erratic behavior may be due to the method of diluting the suspensions of cultural material. The transfer of viable, cultivable material apparently did not invariably occur, as evidenced also by the lack of growth of M. canis in two of the controls.

Summary

Hydrocortisone acetate and alcohol and prednisolone phosphate and alcohol, in the concentrations used, displayed no fungistatic properties against the fungi tested. Candida albicans grew well under conditions adverse to the growth of Trichophyton gypseum, Microsporum audouini, Trichophyton rubrum, and Microsporum canis.

411 Nichols Rd.

Genetic Studies on Acanthosis Nigricans

HELEN OLLENDORFF CURTH, M.D., and BERTHA M. ASCHNER, M.D., New York

In a previous paper by one of us (H. O. C.[1]) the separate character of benign and malignant acanthosis nigricans was stressed. Differences between the two types exist with regard to the age of the patient at the onset of the dermatosis, the course, and the activator of the disorder. It was also pointed out that there may be in the genetic background of the two types significant differences which could furnish additional evidence for the assumption that benign and malignant acanthosis nigricans are separate diseases. The result of our genetic studies has confirmed our early impression.

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From The Department of Dermatology, College of Physicians and Surgeons, Columbia University.

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Since some controversy over the necessity of recognizing different types of acanthosis nigricans has arisen, we shall briefly define benign and malignant acanthosis nigricans before reporting our genetic data on these forms of the dermatosis. Pseudo acanthosis nigricans, a third variety, will also be described, and the reasons for omitting genetic studies on this type will be given.

Benign Acanthosis Nigricans

The term benign acanthosis nigricans has for decades been reserved for that type (Fig. 1) of acanthosis nigricans which is not associated with a malignant tumor. It may be present at birth or begin later, either in childhood or more commonly at puberty. If it appears before that time, it will become more intensified at puberty. This activation of the cutaneous process is most probably due to hormonal imbalance at puberty. After that period, the dermatosis becomes stationary or subsides. It usually is not accompanied by endocrine disturbances in general or by obesity in particular (Fig. 2).

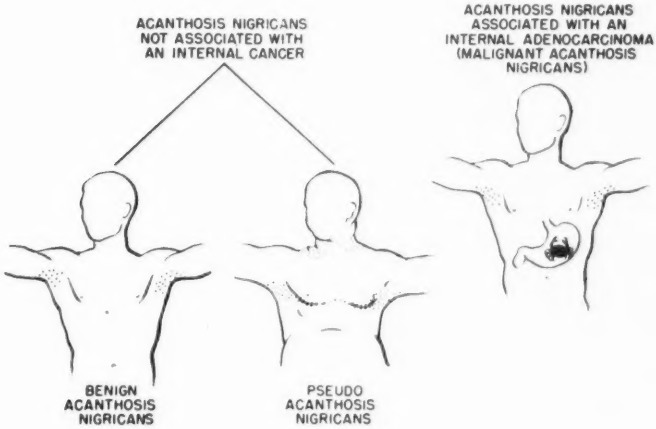
ACANTHOSIS NIGRICANS NOT ASSOCIATED WITH AN INTERNAL CANCER
ACANTHOSIS NIGRICANS ASSOCIATED WITH AN INTERNAL ADENOCARCINOMA (MALIGNANT ACANTHOSIS NIGRICANS)
BENIGN ACANTHOSIS NIGRICANS
PSEUDO ACANTHOSIS NIGRICANS

Fig. 1.—Diagram showing the characteristics of each type of acanthosis nigricans.

Fig. 2.—Benign acanthosis nigricans in a 6-year-old boy.

Fig. 3.—Benign acanthosis nigricans resembling ichthyosis hystrix.

One diagnostic difficulty, the resemblance in some cases between benign acanthosis nigricans and ichthyosis hystrix, must be cited (Fig. 3). It is obvious that classic ichthyosis hystrix shows many features which distinguish it from classic benign acanthosis nigricans. Cases are found, however, representing almost every transitional stage between these two clearly defined extremes. All of these dermatoses, including classic benign acanthosis nigricans and classic ichthyosis hystrix, can be classified as epidermal nevi. Suggestive of ichthyosis hystrix are dry keratoses, the presence of plantar and palmar keratoderma, improvement of the dermatosis in summer, and, histologically, a compact stratum corneum, occasional parakeratosis, and a lack of hyperpigmentation. The epidermis appears massive as compared with its thin and wavy character in benign acanthosis nigricans. The following clinical features are suggestive of benign acanthosis nigricans: a predilection for the axillas, soft ridges, and exacerbation of the dermatosis at puberty. There were five such transitional cases in our group. A sixth patient suffered from benign acanthosis nigricans, as did one of her daughters, while one brother had ichthyosis hystrix with palmar and plantar keratoderma and another brother showed generalized follicular hyperkeratosis.

With the exclusion of these 5 cases resembling ichthyosis hystrix, there remained 13 patients on whom family studies are reported. Among the 13 families were 9 in which more than one member was affected. Altogether, there were 27 instances of benign acanthosis nigricans in these nine families. These figures suggest a genetic background of the disease. There were 14 males and 13 females.

In the literature (Curth,[3] Fladung and Heite,[8] and Hermann [9]) only the benign type has been reported as showing familial incidence. The relatively high familial incidence

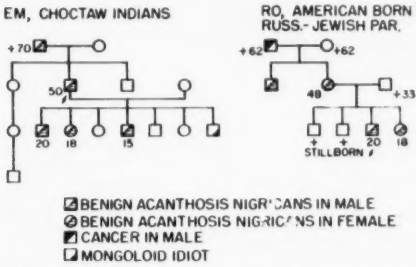
EM, CHOCTAW INDIANS
RO, AMERICAN BORN OF RUSS.- JEWISH PAR.
BENIGN ACANTHOSIS NIGRICANS IN MALE
BENIGN ACANTHOSIS NIGRICANS IN FEMALE
CANCER IN MALE
MONGOLOID IDIOT

Fig. 4.—Pedigrees showing dominant inheritance of benign acanthosis nigricans in three (*EM*) and two (*RO*) consecutive generations.

of a rare hereditary disorder favors the assumption of the dominant mode of inheritance. Dominance as the inheritance pattern was also supported by the transmission of the disorder to consecutive generations. In one pedigree (Em) the dermatosis appeared in three generations, and in two pedigrees (Ro, Mi), in two consecutive generations. In each of these families more than one sibling was affected (Fig. 4).

In several pedigrees, siblings, but not their parents, were affected. Such a picture may be compatible with irregular dominance. In one family (Br) each of three brothers had one affected grandson, including the proband,* but no disease could be detected in the grandfathers themselves or in the following generation. In a disorder as rare as benign acanthosis nigricans, it would be hard to conceive of the possibility that both parents of each of the three affected grandsons carried the injurious gene, a supposition necessary if recessive inheritance is to be assumed. It seems more plausible to infer that the three grandfathers as well as their direct descendants carried and transmitted the injurious gene either without manifesting the dermatosis at all or manifesting it so mildly and for such a short period that the cutaneous changes were overlooked. It is probably no coincidence that the members in whom we discovered the presence of benign acanthosis nigricans were still children or adolescents. Another pedigree (Ma) permits similar conclusions as to irregular dominance. A deceased relative on the proband's mother's side two generations back was supposed to have displayed during her lifetime a dermatosis compatible with benign acanthosis nigricans. No other member of the family besides the proband was affected. In a third pedigree (Ax, Fig. 5) the inheritance pattern can likewise be explained by irregular dominance: The grandfather, who had been married twice, had in each mating some affected grandchildren, among them the proband. The grandfather's brother also had an affected granddaughter.

In our material only one of the probands was the offspring of a marriage of unaffected first cousins (Fig. 6). Although one may consider recessive inheritance in this pedigree, irregular dominance would also explain the inheritance in this family.

There were two additional sporadic cases of benign acanthosis nigricans. In one of them, a seven-year-old girl, the possibility

* A proband is the affected person with whom the genetic investigation originates.

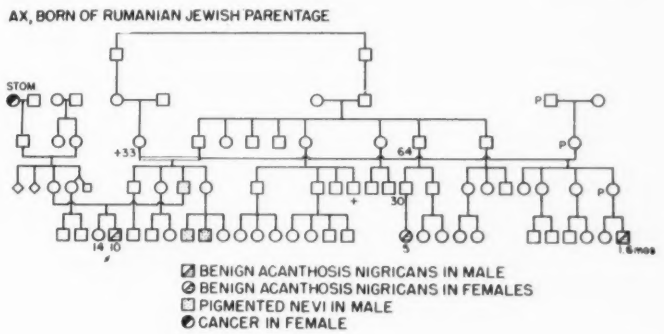
AX, BORN OF RUMANIAN JEWISH PARENTAGE
STOM
BENIGN ACANTHOSIS NIGRICANS IN MALE
BENIGN ACANTHOSIS NIGRICANS IN FEMALES
PIGMENTED NEVI IN MALE
CANCER IN FEMALE

Fig. 5.—The inheritance pattern of benign acanthosis nigricans in this pedigree can be explained by irregular dominance.

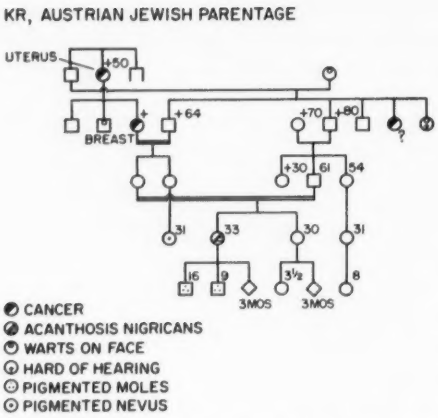

Fig. 6.—33-year-old patient suffering from benign acanthosis nigricans is the daughter of two unaffected first cousins.

of a mutation having occurred in the patient's father had to be considered. All relatives, including the patient's three-year-old sister, were found unaffected. Six years before the proband was born, the father underwent deep x-ray treatment to the scrotum for months, following an operation for seminoma of one testicle. It is probable that the exposure of the remaining testicle to x-rays may have induced a mutation which manifested itself in the following generation. Muller[10] estimated that any new mutation arising after exposure to several hundred roentgens would have a five-to-ten-times-greater probability of having been induced by the radiation than of having arisen spontaneously.

At the 11th International Congress of Dermatology in August, 1957, one of us (H. O. C.) was told by Dr. John V. Klauder, of Philadelphia, that a great number of dogs suffering from acanthosis nigricans were being observed in the Veterinärhogskolan in Stockholm. Dr. Börnfors,[20] the veterinarian in charge, stated that the incidence of acanthosis nigricans in Swedish dachshunds had become a problem to Swedish veterinarians. On examination the diagnosis of acanthosis nigricans seemed correct in several dogs but in others there was the possibility of neurodermatitis. In the future, histological studies will be undertaken to verify the diagnosis of acanthosis nigricans. If this special breed of dogs indeed tends to suffer from acanthosis nigricans, it will provide a rare opportunity to study various problems of heredity of the disease such as the inheritance pattern from the pedigrees of the affected dogs and the results of planned matings of affected with affected and also with nonaffected dogs. The appearance of the disease at an early age in these dogs, the absence of a concomitant cancer, and the high number of familial cases suggests that we are dealing in these animals with benign acanthosis nigricans. Malignant acanthosis nigricans has also been observed in dogs. One of us (H. O. C.) in collaboration with Slanetz[2] described an instance of malignant acanthosis nigricans and cancer of the liver in a dog. We concluded that the similarities between the dermatosis in the human and the canine species far outweighed the dissimilarities, so that it can justly be considered the same disease.

An instance of the unusual combination of unilateral neviform and symmetrical classic benign acanthosis nigricans in one person permitted some speculation as to the genetic character of the unilateral eruption. In this 39-year-old patient (Br)[1] a large acanthotiform nevus, strictly confined to the right side of the abdomen, has been present since birth and has not undergone any changes at any period of his life. At puberty, however, he developed bilateral symmetric benign acanthosis nigricans over wide areas of the body (Fig. 7). These symmetric changes completely subsided after puberty. The unilateral and symmetric eruptions presented an identical histologic picture, that of acanthosis nigricans or epidermal nevus. In determining the genetic character of these eruptions we may apply Siemens'[11] rule, based on morphology: "In general, typically unilateral manifestations are non-hereditary; typically symmetric malformations are usually hereditary." Our patient, however, presented the

Fig. 7.—14-year-old patient with unilateral epidermal nevus present since birth and symmetric benign acanthosis nigricans present since puberty.

unusual combination of this histologically identical, extremely rare dermatosis in unilateral and symmetric distribution. As the symmetric variety has been recognized as a genodermatosis, it seems justified to conclude that both the unilateral and the symmetric eruptions were caused by the same abnormal gene. It must be kept in mind, however, that certain nongenetic factors may have played a role in the determination of the unilateral distribution.

Benign acanthosis nigricans is the sole affliction of many otherwise completely normal persons, but it must be stated that other genetically determined disorders or malformations have often been associated with the disease.[1] It is interesting to note, however, that the degenerative disturbance of the pyramidal tracts, which one of us (H. O. C.) described in a young boy with benign acanthosis nigricans[1] (Case 3), was again observed in identical form in association with benign acanthosis nigricans in an 11-year-old boy by Marañon and Alvarez Cascos.[12] The patient's sister had similar neurologic signs. The authors also studied a young boy, the son of first cousins, who had benign acanthosis nigricans, cirrhosis of the liver, and osseous, ocular, and cardiac malformations. Another one of their patients suffered from diabetes insipidus and arachnodactyly. Johne, Dengler, and Pratje[13] saw acanthosis nigricans, imbecility, and extensive skeletal changes in a girl * who probably had been infected prenatally with toxoplasmosis. A recent report by Ezzo, Rowley, and Finnegan[14] deals with the association of hepatolenticular degeneration with acanthosis nigricans, but because of lack of data on the duration and course of the dermatosis we cannot be sure that this patient suffered from the benign form. One of our female patients † has a rudimentary kidney and ureter and a supernumerary nipple.

How careful one has to be in ascribing the cause of the dermatosis to certain disturbances accompanying acanthosis nigricans can be gathered from the following observation: A girl (Mi) who had suffered from benign acanthosis nigricans since early childhood developed hirsutism and a male

* One of us (H. O. C.) saw this remarkable case in Fürth, Germany.

† This patient[1] (Case 2) had been listed as probably suffering from malignant acanthosis nigricans, although at the time of the report no cancer had developed after six years of observation. In the meantime, six more years have elapsed, and she still shows no sign of cancer. It was contended,[1] however, that "onset of cutaneous lesions at 24 years of age and constant progression of the dermatosis fulfilled the criteria of malignant acanthosis nigricans." Recently, acanthosis nigricans appeared on one of the patient's two daughters and variants of ichthyosis vulgaris were detected in two of her brothers. The patient now remembers that her teachers at school made remarks about her "dirty neck." According to this recent statement and contrary to her previous one, the dermatosis may have started before or at puberty. The patient should continue to be watched for symptoms of cancer, but certain features such as the onset of her dermatosis at or before puberty and the familial involvement bespeak benign rather than malignant acanthosis nigricans.

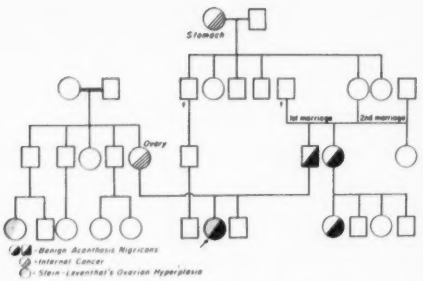

Fig. 8.—Pedigree showing coincidental association of benign acanthosis nigricans with Stein-Leventhal's ovarian hyperplasia in 10-year-old proband.

voice at the age of 10. A connection between the acanthosis nigricans and the distinct endocrine disturbance, which proved to be Stein Leventhal's ovarian hyperplasia, seemed obvious. The pedigree of the family (Fig. 8), however, showed that Stein Leventhal's hyperplasia without acanthosis had occurred in a maternal relative and that benign acanthosis nigricans without ovarian hyperplasia was present in paternal relatives. We must therefore conclude that in this person the association of the two disorders was fortuitous.

Pseudo Acanthosis Nigricans

Pseudo acanthosis nigricans (Fig. 1) is also benign in the sense that it is not associated with a malignant tumor. It is, however, regularly associated with obesity, which may have a nutritional, constitutional, or endocrine basis. The dependence of the dermatosis on obesity is obvious inasmuch as the cutaneous changes start at the time pronounced obesity develops and disappears with the patient's return to normal weight. The name pseudo acanthosis nigricans was applied [4] when it was recognized that this type was not a genodermatosis. Moreover, the cases which led to the concept of this newly recognized entity had insignificant cutaneous changes. This fact continues to be true of the majority of cases (Fig. 9). Slightly elevated dark ridges on the neck and in the axillas of darkly pigmented obese persons are common. Some of the obese

Fig. 9.—14-year-old obese brunette girl showing slight changes of pseudo acanthosis nigricans in right axilla.

patients, among them several with Cushing's syndrome, however, have shown pronounced and rather widespread cutaneous changes. Further studies on patients suffering from pseudo acanthosis nigricans may reveal the basis on which this dermatosis develops and whether mechanical factors alone are responsible for this dermatosis.

Familial cases of pseudo acanthosis nigricans have been observed by W. Jadassohn [15] and one of us (H. O. C.[4]), but this variety was not included in our genetic studies because environmental factors such as food intake and personal hygiene seem to have played a significant role in the pathogenesis of the disorder.

It is tempting to consider pseudo acanthosis nigricans a phenocopy ‡ of benign acanthosis nigricans. If we follow this line of thinking, however, we will have to make the

‡ Phenocopies are pathologic conditions which are similar to those produced by injurious genes but are caused by environmental factors.

same reservations that we must make for any human phenocopy. Not every obese, darkly pigmented person develops pseudo acanthosis nigricans, or, in other words, the identical environmental factor provokes the effect in some, but not in all, persons. We must therefore assume in the affected individual a special disposition which may be of a genetic nature. Moreover, not every case of pseudo acanthosis nigricans resembles the hereditary disease in all respects, and this holds true for other human phenocopies. Such differences are illustrated by the reversibility of pseudo acanthosis versus the relative irreversibility of benign acanthosis nigricans and by the dependence of benign acanthosis nigricans on hormonal influences at puberty, whereas pseudo acanthosis nigricans remains uninfluenced by these hormones.

Malignant Acanthosis Nigricans

Malignant acanthosis nigricans (Fig. 1) is always associated with an internal malignant tumor. This statement is not invalidated by the fact that in a few of the reported cases the presence of the cancer has not been demonstrated or the patient died before manifestation of the cancer. The dermatosis begins before, at the time of, or after manifestation of the cancer. It increases in severity with the propagation of the cancer, but it has in many instances shown temporary regression after operation or irradiation of the tumor. Malignant acanthosis nigricans resembles the other types of acanthosis nigricans, but in some instances involvement of the oral cavity and the occurrence of palmar and plantar keratoses have been noteworthy. The dermatosis usually occurs in adults, but a few instances of malignant acanthosis nigricans in children have been reported.

Genetic Data.—No other case of malignant acanthosis nigricans has been found in the families of patients investigated by us or reported in the literature.[1-8] This fact does not entirely abrogate the assumption that it is a genetically determined disease. In rare, recessively inherited disorders, the mating of partners each carrying the abnormal gene may be a very unusual event, and, even if it does take place, only one-quarter of the offspring can be expected to show the trait. If the disturbance is dependent on multiple rare genes, the probability of familial occurrence would be low. The fact that the disorder has not shown up in more than one sibling tends to rule out fully penetrant genes of recessive or dominant character and to suggest low penetrance, complex multigenic inheritance, an undetermined nongenetic factor or a combination of environment and genetic background.

There was one consanguineous marriage (Fig. 10) among the parents of the 26 patients suffering from malignant acanthosis nigricans. If a significant percentage of consanguineous marriage of the probands' parents were observed in a much larger series, it might suggest recessive inheritance of the disorder.

Two pedigrees illustrate some of the difficulties we encountered in compiling our data. Excellent records were available for the family of one proband's father, which had resided in a small town of Southern Germany for several hundred years, but the mother was an illegitimate child; little information could be obtained about her mother and none about her father. The pedigree (Fig. 11) of a Quaker family could be traced back to the year 1681 and showed numerous consanguineous marri-

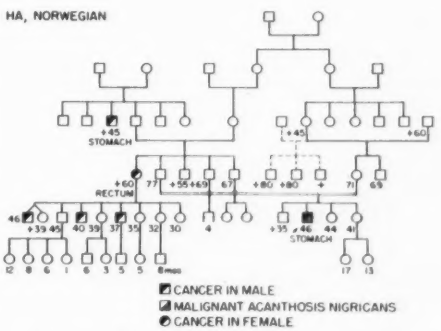

Fig. 10.—Proband suffering from malignant acanthosis nigricans is the son of second cousins.

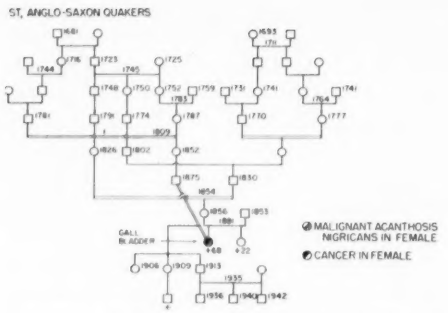

Fig. 11.—Pedigree going back to year 1681 and showing numerous consanguineous marriages in the ancestry of the proband's mother. Proband suffered from malignant acanthosis nigricans.

ages in the ancestry of the proband's mother, but, unfortunately, no record could be found as to the origin of the proband's father and whether he was related to his wife's family. The proband herself married a relative on her mother's side, but none of her progeny, three children and four grandchildren, have so far shown the disease.

Incidence of Cancer in Relatives of Patients with Malignant Acanthosis Nigricans.

Besides searching for familial cases of malignant acanthosis nigricans, which were never found, we noted the frequency of cancer in family members of probands with malignant acanthosis nigricans. The Table shows the location of the cancers in the probands and their relatives.

With regard to the type of tumor of the proband, 61% of cancers associated with malignant acanthosis nigricans in this group were gastric. This percentage of gastric cancer is the same as that found by Fladung and Heite [8] in a larger series and compares well with the figures of 62% [3] or 64% [5] that one of us (H. O. C.) obtained from two large series of cases. The percentage of gastric cancers associated with malignant acanthosis nigricans in this series is high as compared with the frequency of gastric cancer in the population at large. When gastric cancer occurred in the proband this type of tumor was also found in one relative of Cases 3, 4, and 6 and in several relatives

Cancer in Relatives of Patients Suffering from Malignant Acanthosis Nigricans

	Cancer in Patient		Cancer in Relative	
Case	Site	Sex	Site	Relative
1	Bronchial	M	Gastric	1 Paternal
2	Gastric	F	Unspecified	1 Paternal
3	Gastric	F	Gastric	1 Paternal
4	Gastric	F	Gastric	1 Maternal
5	Gastric	M	G. i. tract	3 Maternal
6	Gastric	M	Gastric	1 Paternal
			G. i. tract	1 Paternal
			Unspecified	3 Paternal
7	Gastric	F	Gastric	4 Paternal
			(G. i. symptoms	3 Paternal)
			Liver	1 Maternal
			Mammary	1 Maternal
8	Gastric	F	Mammary	3 Maternal
			Prostate	1 Maternal
			Unclassified	1 Maternal
			Hodgkin, disease	1 Maternal
9	Ovarian	F	Retroperitoneal sarcoma	Sister
10	Mammary	F	Uterine	1 Maternal
			Mammary	1 Paternal
11	In hilar lymph node; primary site unknown	M	Unspecified	2 Maternal
12	Gastric	M	Malignant melanoma or rhabdomyosarcoma	Niece
13 to 26*	8 gastric	6 M, 2 F		
	1 pancreatic	F		
	2 bronchial	2 M		
	1 ovarian	F		
	1 sigmoid	M		
	1 of gall bladder	F		

* No cancer in relatives.

of Cases 5 and 7. Case 7 is of particular interest because four paternal relatives had gastric cancer and three young paternal relatives had gastrointestinal symptoms. These findings are somewhat comparable to those of Levin and Kuchur [16] in that relatives of patients with gastric cancer showed a higher incidence of gastric cancer and achlorhydria than did controls. In contrast to involvement limited to the stomach and gastrointestinal tract observed in the paternal relatives, two maternal relatives of Case 7 had cancer, one of the liver and the other of the breast. Hagy,[17] whose results paralleled those of Levin and Kuchur [16] and Macklin [18] with regard to the frequency of gastric cancer in the relatives of probands with gastric cancer, found in addition a significantly higher frequency of cancer of the gastrointestinal tract in rela-

tives of probands with gastric cancer than in his control material. Case 6, a proband with gastric cancer, had one paternal relative with cancer of the gastrointestinal tract, three with unspecified cancer, and one with gastric cancer. The question arises why all these relatives with gastric cancer did not also show malignant acanthosis nigricans. We have to speculate either that the types of gastric cancer in the probands and their relatives were different or that the probands with gastric cancer differed from their relatives with gastric cancer with regard either to a genetic background for malignant acanthosis nigricans or to some as yet undetermined environmental factor. Mammary cancer as in Proband 10 also occurred in her mother, and uterine cancer, in her maternal grandmother. Instances of cancer in sites other than those of the proband were seen in Cases 1, 8, and 11. Hodgkin's disease and malignant melanoma, malignant processes, not of adenocarcinomatous character, were observed in one relative of each of two probands (Cases 8 and 12) with gastric cancer. A retroperitoneal sarcoma occurred in the sister of a patient with ovarian carcinoma (Case 9).

No malignant tumor was found in the relatives of Cases 13 to 26, i. e., in 54% of the group, although 8 of these 14 patients had gastric cancer. This series, however, is too small to permit speculation as to the reasons for the absence of familial cancer in probands with gastric cancer.

In trying to ascertain whether one side or both sides of the probands' family showed a significant incidence of certain cancers, we found only in Case 7 a considerable number of cancers on both sides of the family.

Ethnic Background.—The geographic-ethnic origin of all patients with malignant acanthosis nigricans was scrutinized in an effort to uncover additional evidence of recessive inheritance of the disease. There were several instances in which the proband's mother and father were born in the same community in Eastern or Western Europe, but no relationship between the parents could be definitely established. In all but 2 of the 26 families the proband's father and mother had an identical ethnic background. They were French Canadians (1), Italians or Americans of Italian stock (2), Russian Jews (2), Hungarian Jews (1), Galician Jews (1), Polish Jews (1), German Jews (1), Germans or Americans of German stock (3), Norwegians (2), Scandinavians (1), Ukrainians (1), Austrians (1), Anglo-Saxons or Americans of Anglo-Saxon stock (6), and American Negroes (1). In one of the two remaining families the ethnic backgrounds of the father and the mother were not far apart. The father came from Alsace-Lorraine, and the mother was born in the U. S., probably of German stock; in the other, however, one parent came from Alsace-Lorraine and the other from Ireland. Although our series is too small to warrant drawing conclusions as to the ethnic background of the patients, we are of the opinion that this aspect of the study warrants further attention.

The Association of Malignant Acanthosis Nigricans with Cancer.—Malignant acanthosis nigricans, although invariably associated with an internal cancer, was, as a rule, not accompanied by malformations or hereditary disorders. Extensive pigmented nevi, however, were observed in two members of one family and in one member of another.

The constant association of malignant acanthosis nigricans and cancer rules out a chance relationship between the two but does not offer a clue as to the nature of the relationship. It is still doubtful whether either the whole syndrome or even one part of it is inherited. Let us consider the possibilities of inheritance (Fig. 12) of (*A*) the dermatosis alone, (*B*) the cancer alone, (*C*) the dermatosis and the cancer.

(*A*) Inheritance of the gene responsible for the dermatosis would lead to its expression only in the presence of a coincidentally occurring cancer. In the absence of the

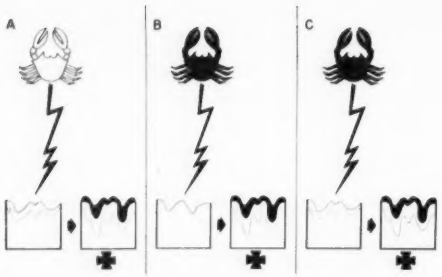

Fig. 12.—Diagram illustrating the possibilities of inheritance of the components of malignant acanthosis nigricans. Inheritance of (*A*) the dermatosis alone, (*B*) the cancer alone, and (*C*) the dermatosis and the cancer.

cancer, on the other hand, the dermatosis would not be expressed. Implied in this concept is the assumption that the cancer capable of activating malignant acanthosis nigricans is the same tumor that occurs in the general population.

(*B*) Concept (*B*) envisages the inheritance of the cancer alone, which in turn would cause the appearance of acanthosis nigricans. Clinical observations show a definite parallel between the course of the tumor and that of the dermatosis, and this speaks in favor of Concept (*B*). Whether activity of a tumor, however, can have a dermatosis-producing effect if the person does not possess the genetic disposition for the dermatosis remains questionable.

(*C*) The concept that both the cancer and the dermatosis are inherited finds support in the fact that the two manifestations of the syndrome, the internal cancer and the acanthosis nigricans, represent epithelial hyperplasia, malignant in one and benign in the other.

Concepts (*B*) and (*C*), which postulate a genetic origin for the cancer, are based on the assumption that we are dealing in all cases of malignant acanthosis nigricans with one type of tumor. It would seem at first glance that the various sites of origin of these tumors—stomach, esophagus, intestines, rectum, liver, pancreas, gallbladder, uterus, ovary, lung, mammary gland (and thyroid ?)—rather militate against a concept of uniformity. We must admit, moreover, that biochemical characteristics which might distinguish tumors associated with acanthosis nigricans from those which are not have not as yet been uncovered. It has been found, however, that tumors associated with acanthosis nigricans, although they originate in different organs, show identical clinical and pathologic attributes.

The tumors in question are highly malignant. Not a single patient's life has been saved, because of early metastasis or inoperability of the tumor. After the onset of the disease the duration of life was short. This was determined by two different methods. One of us (H. O. C.[1]) measured the period until death from the discovery of the tumor, and Fladung and Heite,[8] from the beginning of the dermatosis.

The tumor associated with malignant acanthosis nigricans is an adenocarcinoma. In a study of the pathologic aspects with Drs. H. L. Stewart and A. W. Hilberg, of the National Cancer Institute, of Bethesda, Md., slides of 25 tumors associated with malignant acanthosis nigricans were reviewed.[7] In one case there was a possibility of reticulum-cell sarcoma, but metastatic carcinoma could not be ruled out. Twenty slides showed adenocarcinoma. The remaining four showed cancer, but the material was inadequate to permit a definite classification of the tumor.

While neither the pathological nor the clinical attributes of these tumors are unique, further investigation may yet establish their specificity.§

If we assume a genetic basis for the syndrome of malignant acanthosis nigricans, the fact that the dermatosis has always been accompanied by cancer is evidence for a pleiotropic gene, i. e., a gene with multiple effects, and not for linkage. For if the association were due to linkage, then crossing over, a frequent occurrence of interchange of parts of the chromosomes during cell division, would have led to the separa-

§ The pathology of this series of tumors and of those reported by other authors will be discussed in another paper.

tion of malignant acanthosis nigricans and cancer in some gametes. But can we state with reasonable certainty that acanthosis nigricans and cancer have never been separated? We cannot be sure whether this particular cancer does occur without acanthosis nigricans because we lack knowledge of the biochemical qualities identifying the tumor associated with acanthosis nigricans, and we are ignorant as to whether these biochemical substances are limited to the tumor accompanying the dermatosis. We are, however, reasonably certain that malignant acanthosis nigricans does not occur without the cancer. Under no circumstances can benign acanthosis be considered in this connection to represent "acanthosis nigricans without cancer." The benign type is an entity entirely separate from malignant acanthosis nigricans. In the introduction to this paper we pointed out the differences between the two types. To these differences can now be added those of the genetic background. Furthermore, the fact that no instance of transition from the benign to the malignant form or of occurrence of both types in one family has ever occurred confirms the duality of benign and malignant acanthosis nigricans.

Summary

Of the three types, benign, pseudo, and malignant acanthosis nigricans, a genetic basis has been ascertained only for the benign type, which shows either regular or irregular dominance. Pseudo acanthosis nigricans, secondary to excessive obesity, may be considered a phenocopy of benign acanthosis nigricans. No familial case of malignant acanthosis nigricans has been found. Among the 26 pedigrees of malignant acanthosis nigricans, one consanguineous marriage of the proband's parents was found. Our series of families is too small to permit us to consider this incidence as an indication of recessive inheritance of malignant acanthosis nigricans. Family members of patients suffering from malignant acanthosis nigricans were examined also for cancer without acanthosis nigricans. No specific trend with regard to frequency and location of tumors in the relatives of the 26 probands was seen, and no cancer occurred in the relatives of 54% of these probands. In 24 of the 26 probands suffering from malignant acanthosis nigricans, both parents had an identical ethnic background. The possibility of a genetic basis for the whole syndrome of malignant acanthosis nigricans or for part of it is discussed. The tumors associated with malignant acanthosis nigricans, although originating in various organs, show similar clinical behavior and similar morphology in that they all are adenocarcinomas; the specificity of these tumors, however, has not as yet been established. The percentage of gastric cancers among the cancers associated with malignant acanthosis nigricans was high.

Many physicians gave permission to have their patients or their patients' families investigated.

35 E. 84th St. (28).

REFERENCES

1. Curth, H. O.: Significance of Acanthosis Nigricans, A. M. A. Arch. Dermat. & Syph. 66: 80-100 (July) 1952.

2. Curth, H. O., and Slanetz, C. A.: Acanthosis Nigricans and Cancer of the Liver in a Dog, Am. J. Cancer 37:216-223 (Oct.) 1939.

3. Curth, H. O.: Benign Type of Acanthosis Nigricans: Etiology, Arch. Dermat. & Syph. 34: 353-366 (Sept.) 1936.

4. Curth, H. O.: Pseudo-acanthosis nigricans, Ann. dermat. et syph. 78:417-429 (July-Aug.) 1951.

5. Curth, H. O.: Acanthosis Nigricans and Its Association with Cancer, Arch. Dermat. & Syph. 57:158-170 (Feb.) 1948.

6. Curth, H. O.: Acanthosis nigricans und Krebs, Ztschr. Krebsforsch 56:307-328, 1949.

7. Curth, H. O.: Dermatoses and Malignant Internal Tumors, A. M. A. Arch. Dermat. 71:95-107 (Jan.) 1955.

8. Fladung, G., and Heite, H. J.: Häufigkeitsanalytische Untersuchungen zur Frage der symptomatologischen Abgrenzung verschiedener Formen der Acanthosis nigricans, Arch. klin. u. exper. Dermat. 205:282-311, 1957.

9. Hermann, H.: Zur Erbpathologie der Acanthosis nigricans, Ztschr. menschl. Vererb.- u. Konstitutionslehre 33:193-202, 1955.

10. Muller, H. J.: Personal communication to the authors.

11. Siemens, H. W.: Die Vererbung in der Ätiologie der Hautkrankheiten, in Handbuch der Haut- u. Geschlechtskrankheiten edited by J. Jadassohn, Springer-Verlag, 1929, Vol. 3, p. 43.

12. Marañon, G., and Alvarez Cascos, M.: Die gutartige jugendliche "Acanthosis nigricans": Ihr Zusammenhang mit den angeborenen Missbildungen, Acta dermat.-venereol. 37:249-253, 1957.

13. Johne, H. O.; Dengler, H., and Pratje, A.: Zum Studium der Acanthosis nigricans, Arch. klin. u. exper. Dermat. 201:36-48, 1955.

14. Ezzo, J. A.; Rowley, J. F., and Finnegan, J. V.: Hepatolenticular Degeneration Associated with Acanthosis Nigricans, A. M. A. Arch. Int. Med. 100:827-832 (Nov.) 1957.

15. Jadassohn, W.: Familiäre Acanthosis nigricans kombiniert mit Fettsucht, Arch. Dermat. u. Syph. 150:110-114, 1926.

16. Levin, A. E., and Kuchur, B. A.: An Investigation of the Relatives of Patients with Gastric Cancer, Lancet 1:204-205, 1937.

17. Hagy, G. W.: A Familial Study of Gastric Carcinoma, Am. J. Human Genet. 6:434-447 (Dec.) 1954.

18. Macklin, M. T.: Inheritance of Cancer in Man, Schweiz. Ztschr. allg. Path. 18:463-471, 1955.

19. Macklin, M. T.: The Role of Heredity in Gastric and Intestinal Cancer, Gastroenterology 29:507-511, 1955.

20. Börnfors, S.: Acanthosis Nigricans in Dogs: A Study of Etiology and Medical Treatment with Special Attention to Hypophyseal Thyroid Function, Acta endocrinol., Supp. 37:37, 1958.

The Basal-Cell Nevus

Its Relationship to Multiple Cutaneous Cancers and Associated Anomalies of Development

J. B. HOWELL, M.D., Dallas, Texas, and MARCUS R. CARO, M.D., Chicago

The basal-cell nevus is a dysgenetic dermatosis characterized by multiple small cutaneous tumors. These are histologically indistinguishable from basal-cell cancer. Malignant supervention is common, generally resulting in multiple basal-cell cancers of the face in young adults. Developmental defects of other systems are often present. Incidence seems to be based on an inherited, sometimes familial, predisposition.

Clinical Features

Basal-cell nevi may appear at birth or be first noted in infancy. Occasionally the lesions may begin at about puberty and gradually increase in number and in size over a period of years. There may be few or hundreds, and there is a tendency for bilateral distribution, but this need not be symmetrical. The size of the individual lesion varies from that of a pinhead to approximately 5 mm. in diameter. Pedunculated and papular lesions are common on the neck, eyelids, and axillae.

The color is that of the surrounding skin, but the lesions may be hyperpigmented. The individual lesions are elevated, firm, symptomless, and painless to the touch. Their surface is smooth, and occasionally it may be covered by minute blood vessels or by one or more minute white milium-like bodies. They vary greatly in distribution. By far the largest number of lesions have been observed over the trunk and extremities. The gross resemblance to neurofibromas may be striking, as shown in the case presented by Rodin.[1] A unique case of linear unilateral systematized basal-cell nevus with comedones was reported by Carney.[2]

The center of the face and the neck are often involved; the eyelids, the nose, the cheeks, the preauricular and postauricular areas, and the neck are common sites of predilection. The forehead may have a number of lesions, but the scalp is seldom involved. Ulceration does not ordinarily occur and, when observed, is usually indicative of malignant supervention. We found no reports of a solitary basal-cell nevus, but this occurrence is possible.

Associated Anomalies of Development

Binkley and Johnson[3] called attention to partial agenesis of the corpus callosum, multiple dental follicular cysts, a bifid sixth rib, a fibroma of the ovary, and a fatty tumor of the left foot as accompanying anomalies of development in their patient with basal-cell nevi. Identical cutaneous lesions were found in one of the patient's five children. This daughter, aged 6 years, had multiple basal-cell nevi without other developmental defects. A psychometric examination revealed a normal mentality.

Gross[4] reported a similar case of a boy with multiple basal-cell nevi located chiefly on the torso and extremities. He also had follicular cysts of the maxilla and mandible, synosteosis of the left first rib, and a bifid left and right sixth rib. Carney's patient with linear unilateral basal-cell nevus and comedones had in addition a marked congenital dorsal scoliosis.

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Clinical Assistant Professor of Dermatology and Syphilology, Southwestern Medical College, University of Texas (Dr. Howell).

Fig. 1 (Case 1).—Epithelial cysts on the volar surface of the left thumb and the left fourth finger.

In one of our patients there are benign cystic lesions of the mandible and a small congenital anomaly of the left fourth rib anteriorly, showing an attempt at bifurcation. There are multiple epithelial cysts on the scalp, the face, the neck, the right ankle, and the palmar surface of the left thumb and the fourth finger (Fig. 1). Milia are numerous on the face. Only one of this patient's four children has basal-cell nevi. The epithelial cysts, cysts of the mandible, and multiple skin cancers are common to several brothers, nieces, and nephews in this family.

Multiple Cutaneous Cancers

Multiple destructive, devouring, and disfiguring cutaneous cancers may develop from basal-cell nevi, but they may also occur associated with, but independent of, them. This is an important and significant feature of this syndrome. Rodent ulcers develop in the early decades as well as in the later years in patients with this dermatosis. The carcinomas are generally multiple slow-growing tumors with a relentless course. One should stress in these patients the potential danger of partial or complete destruction of the eyelids, with a subsequent loss of one or both eyes, as has been emphasized by Norman Paul.[5] Likewise, the nose may be in danger of partial or complete destruction by the numerous cutaneous cancers.

All basal-cell nevi of the eyelids, nose, and nasolabial furrows should be completely removed. These sites should be inspected at frequent intervals and any recurrent or new lesions removed. Malignant change may take place slowly in a few lesions over the years, or there may be an accelerated development of multiple rodent ulcers.

Nomland [6] was the first to report multiple basal-cell cancers developing from pigmented basal-cell nevi in adult life. He recognized the condition to be unique, and he pointed out that these nevi differed from ordinary pigmented intradermal nevi and from epithelioma adenoides cysticum. From a study of the protocols of the patients reported as having multiple cutaneous cancers associated with epithelioma adenoides cysticum, we believe that it is doubtful that the multiple rodent ulcers developed from lesions of epithelioma adenoides cysticum. Perhaps some of these were multiple basal-cell cancers secondary to the basal-cell nevus. Adamson [7] likewise proposed excluding from the group of epithelioma adenoides cysticum the patients reported by Jarisch [8] and White,[9] because of the development of multiple rodent ulcers in these cases. The patients reported by Stelwagon and Gaskill,[10] Pautrier and Archambault,[11] Little,[12] and Ormsby [13] seem to warrant a similar exclusion. The occurrence of multiple primary rodent ulcers of the face is well known, and this condition should be distinguished from the disorder under discussion.

It is our impression that rodent ulcers develop more often from basal-cell nevi situated on the face and neck. Multiple rodent ulcers in association with basal-cell nevi have been observed by Nomland,[6] Nisbit,[14] Binkley and Johnson,[3] Carney,[2] Wooldridge,* and Mueller,[15] and most of these were present on the face and neck. We believe this combination is a frequent one which should be expected in patients with basal-cell nevi on the face and neck.

* Case 4, included in this report.

Report of Cases

CASE 1.—A 59-year-old schoolteacher for approximately 40 years has had multiple skin tumors of the face distributed primarily about the nose and eyelids (Fig. 2). When he was 27 the first lesion that was considered a skin cancer was removed. Thereafter, at intervals of a few years, increased growth or ulceration of an existing lesion occurred and necessitated treatment. Rodent ulcers developed with greater frequency, and they became multiple in 1947.

In June, 1929, when the patient was 30, an upper left canine was removed because of pain. This was followed by the separation of a large sequestrum of bone, making an opening into the left maxillary sinus large enough to admit two fingers. The sinus was found to be filled with a bluish mass which the pathologist at first reported to be chronic inflammatory tissue. The left maxillary sinus was then extirpated, and the site healed uneventfully. On studying the surgical specimen the pathologist favored a diagnosis of sarcoma, and radium was used subsequently in the antrum.

Later in 1929, a large portion of the hard palate on the left side was removed at the Mayo Clinic and the antrum was explored, with resection of devitalized bone. No evidence of malignant disease was found. In 1933, at the Mayo Clinic, a cyst of the left mandible was also removed and approximately 30 small tumors which clinically appeared to be basal-cell epitheliomas were electrocoagulated. The largest of these lesions was situated in the right mastoid region, and this was excised. Histopathologically, this lesion was reported to be a mixed basosquamous-cell epithelioma, Grade I.

In 1951, a dentigerous cyst was removed from the angle of the left mandible. The pathologist reported that the cyst had a thick layer of connective tissue lined by stratified squamous epithelium. The cyst wall showed numerous foci of pus cells, lymphocytes, and eosinophils. No anaplasia of cells was seen, and a diagnosis of infected dental cyst was made.

In August, 1953, the patient was seen by one of us (J. B. H.) for a slowly growing invasive rodent ulcer of three years' duration involving the left medial canthus and the upper and lower eyelids. He had many other rodent ulcers on the face, neck, and ears and a few on the sternum and shoulders. During the next three years an attempt was made to destroy the numerous lesions. Roentgen therapy was used on the lesion of the left medial canthus and the right upper lip area (78 kv.; half-value layer 1.65 mm. Al; 4900 r given in divided doses of 700 r every second day for seven treatments). Low-content radium needles were used on a large lesion of the right cheek,

A
B

which was found to have infiltrated so deeply that complete destruction by electrosurgery was considered impractical.

From 1953 to 1956, approximately 50 lesions were destroyed by electrocoagulation and curettement. In November, 1955, persistent carcinoma was demonstrated in the left medial canthus where x-ray therapy had been administered. In addition a progressive rodent ulcer was noted on the central portion of the right lower eyelid. Chemosurgery was advised, but this was delayed until the summer of 1956.

In June, 1956, Dr. Frederic Mohs treated approximately 35 basal-cell cancers by chemosurgery. He reported that the most difficult lesion was this deep-seated ulcerated mass of the left medial canthus, with induration about 2 cm. in diameter and with obvious extension into the medial portion of the upper and lower eyelids and to the bulbar conjunctiva. The basal-cell carcinoma was found to extend against the sclera, but it did not penetrate its full thickness. It also extended into the lacrimal sac and for considerable distance just underneath the conjunctiva of the upper and lower eyelids. Some of the medial rectus muscle was involved, but not enough to interfere with its function. A tarsorrhaphy was performed to the region of the limbus in order that the patient could have the use of his left eye while the right lower eyelid was under treatment. The lesion on the right lower eyelid was a rather deep basal-cell carcinoma extending through the conjunctiva, making it necessary to remove the full thickness of the eyelid. In addition the tumors on the left side of the nose were treated and found to extend through the full thickness of the ala and the bridge.

The chemosurgery was successful in saving the left eye, which was quite an accomplishment. During the past six months new cancers have developed, with approximately 20 on the face and 8 on the back at this time. These are now being destroyed at regular intervals by electrosurgery.

CASE 2.—A boy, aged 11, was examined first in July, 1955, because of numerous small tumors on the neck, preauricular areas, eyelids, and nose (Fig. 3). His father was concerned because he recognized that his son had the same type of cutaneous tumors that he himself had acquired at a comparable age. The mental and physical development of this boy as judged by his school career and physical growth has been normal, and x-ray evidence of maxillary or mandibular cysts or bifid ribs was absent.

A diagnosis of multiple basal-cell nevi was made clinically. Four of the tumors had exhibited accelerated growth in recent weeks and were suggestive of early basal-cell cancers. These were located on the left lower eyelid, the right medial canthus, the left nasolabial fold, and the left side of the neck. Specimens for biopsy were taken from the tumors of the eyelid regions only. Then all four lesions were destroyed by electrosurgery. The pathologist's diagnosis of both specimens from the eyelid was basal-cell carcinoma. The sites where the basal-cell carcinomas were destroyed have remained well.

One month later approximately 10 of the basal-cell nevi were destroyed by electrosurgery. During the following two years all of the detectable basal-cell nevi were destroyed by liquid nitrogen or electrosurgery. None of these lesions had shown accelerated growth or ulceration. Whether new lesions are developing is difficult to determine because the rate of development of new nevi is exceedingly slow. A long-range program, therefore, has been undertaken to observe the patient and to destroy all of the basal-cell nevi soon after they appear.

CASE 3.—A white girl, aged 10, first developed lesions on her chest at about one year of age. New lesions appeared in rapid succession, and they varied in appearance from tiny, firm, clear, semiglobular papules to brownish, soft, flat, or pedunculated papules up to 5 mm. in diameter. When she was presented before the Chicago Dermatological Society on Feb. 15, 1950, by Dr. H. H. Rodin, at the age of 2½ years, there were over 100 lesions present on the front and back of the chest, the neck, and the shoulders and a few on the eyelids (Figs. 4A and 4B). The clinical appearance suggested the diagnosis of neurofibroma, but an examination of sections from a tiny lesion and a larger pedunculated papule showed the histopathologic features of a basal-cell epithelioma.

During the past eight years new lesions have continued to appear, and there are now hundreds of papules on the neck, all around the chest, on the axillae, and on the abdomen and a few on the eyelids and nose (Figs. 5A and 5B). These vary in size from 1 mm. to 8 mm. in diameter, many are semi-globular and the larger ones are either sessile or pedunculated (Fig. 5C). The surface of each is smooth and the color varies from that of her normal skin to a brownish hue. Occasionally even a slight injury to a lesion has caused profuse bleeding from the traumatized base.

Five lesions were removed for examination and sections from each showed the histopathologic features of basal-cell epithelioma.

During the past few years six dentigerous cysts were removed from her mandible and maxilla, but we have found no evidence of any other developmental anomalies. Her mother has many seborrheic keratoses on her body, but her father is free from cutaneous lesions. There are no siblings.

Figs. 4A and 4B (Case 3).—Front and back views of the chest taken in 1950, at the age of 2½ years.

Figs. 5A and 5B (Case 3).—Front and back views taken in 1958, at the age of 10 years.

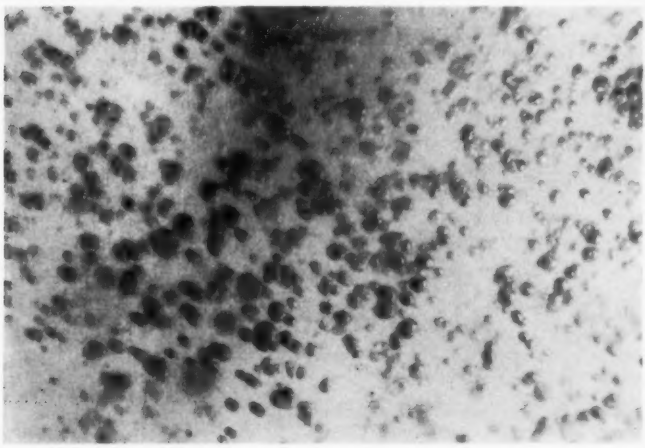

Fig. 5C (Case 3).—Close-up of lesions on the front of the chest (1958).

CASE 4.—A patient of Dr. Wilfred Wooldridge † developed papular lesions about the eyelids, the neck, the face, and the shoulders at about the age of 2 years. The lesions were flesh-colored and soft. In the course of several years the lesions enlarged with brownish pigmentation, and from time to time new ones appeared. On July 5, 1950, a pedunculated lesion was excised from the right shoulder for biopsy. The pathologist, Dr. John Frerichs, reported basal-cell carcinoma, probably of nevoid origin and benign. Dr. Frerichs remarked that although the tissue histologically was basal-cell carcinoma, he did not believe that it would behave as a malignant growth. The patient, when 8 years old, was presented (in 1950) at the Dermatology Clinic of the Southern Medical Association Meeting, at St. Louis, as having multiple benign cystic epitheliomas without family history

† Included through the permission of Dr. Wilfred Wooldridge, of Springfield, Mo.

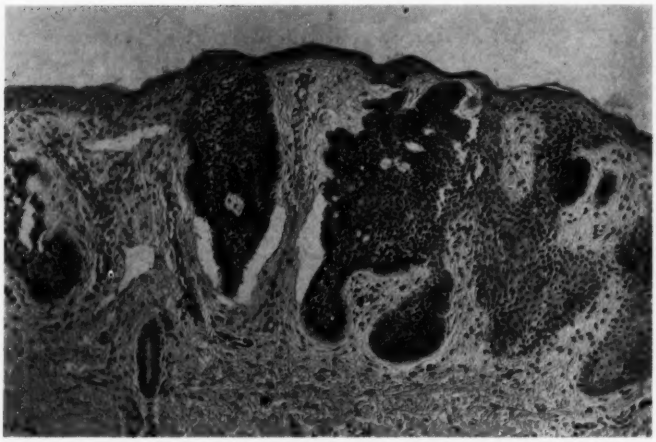

Fig. 6A (Case 3).—Section from tiny lesion removed in 1950, showing small buds of deeply staining basal cells attached to the undersurface of the epidermis. Hematoxylin and eosin; reduced 40% from mag. × 160.

of the disease. Examination disclosed the eyelids, face, neck, and shoulders to be covered with innumerable lesions varying in size from that of a pinhead to 3 mm. in diameter. There were no lesions found on the lower portions of the body. The discussion elicited great confusion because of the discrepancy between the benign gross appearance of the lesions and the histopathologic features of basal-cell cancer.

Over the years many small lesions were treated with liquid oxygen, and practically all of these have remained well. Because of the great number of lesions that developed on the neck and the upper portion of the trunk, these areas were treated by planing in March and April, 1955, and these too have remained well. In 1957, the patient, now 15 years old, returned to Dr. Wooldridge with lesions on the right side of the nose and on the right temple which had shown consistent growth. These lesions were excised, and both were reported as being basal-cell carcinomas.

Histopathologic Features

The most striking feature of this entity is the wide discrepancy between the histopathologic findings in even the earliest lesions and the clinical appearance of the lesions. In the smallest papules present, as well as in the largest and oldest ones, the sections show sharply outlined nests of densely packed and deeply stained basal cells. These may form small buds that are attached to the under surface of the epidermis (Fig. 6A) or at times anastomosing strands of basal cells that fill the corium (Fig. 6B). In some lesions there are large densely packed cellular masses (Fig. 6C), and in others these develop cyst-like spaces (Fig. 6D). In several lesions there are

Fig. 6B (Case 3).—Section from larger papule removed in 1950, showing anastomosing narrow strands of basal cells lying in a stroma of vascular connective tissue. Hematoxylin and eosin; reduced 40% from mag. × 45.

Fig. 6C (Case 2).—Section from papule on face, showing large densely packed mass of basal cells with cyst formation, considerable pigment, and a vascular connective tissue stroma. Hematoxylin and eosin; reduced 40% from mag. × 160.

many lattice-like strands of basal cells, and, in the predunculated papules, these strands extend throughout the entire corium (Fig. 6E). In many of the sections there are numerous dilated blood vessels present throughout the corium, and these no doubt account for the ready bleeding from the lesions following injury. Melanin pigment was demonstrated in many of the sections, both in the tumor masses and in the intervening corium.

All of these histopathologic findings are identical with those seen in sections from frank basal-cell cancers (Fig. 6F). One cannot distinguish from the section alone which was taken from an early lesion and which from an older one. Neither can one differentiate with certainty a section from a lesion that is still clinically benign from one that has already become invasive and malignant.

Sections from lesions of basal-cell nevus can be differentiated from those of multiple benign cystic epithelioma by the absence of horn cysts and of abortive hairs. Premalignant fibroepithelial tumors of the skin (Pinkus) are distinguished by the excessive formation of fibrous connective tissue, a feature that was not seen in our sections.

Treatment

Treatment may be both prophylactic and definitive. Prophylactic treatment of the nevi as a means of preventing cancer is

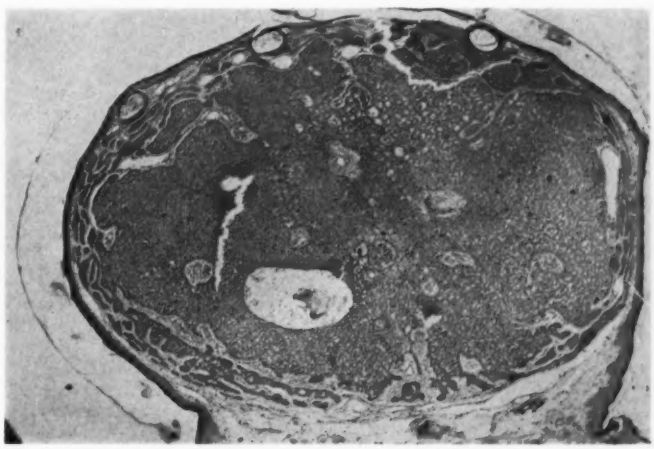

Fig. 6D (Case 2).—Section from papule on the left lower eyelid, showing sharply circumscribed tumor mass composed of densely packed basal cells with considerable cyst formation. Hematoxylin and eosin; reduced 40% from mag. × 45.

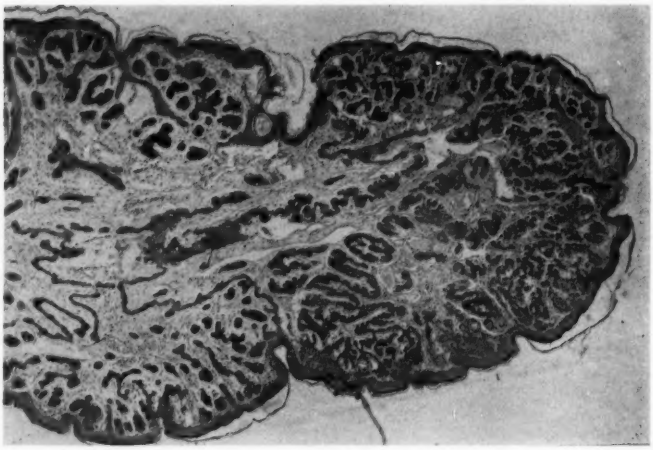

Fig. 6E (Case 3).—Section of pedunculated papule removed in 1958, showing many anastomosing filigree-like strands of basal cells lying in a very vascular connective tissue. Hematoxylin and eosin; reduced 40% from mag. × 45.

highly desirable, especially in the region of the eyelids and nose. All basal-cell nevi on these areas should be removed or completely, yet conservatively, destroyed. This may be accomplished adequately by cautery, electrosurgery, excision, or freezing with liquid oxygen or nitrogen. In some instances there are so many lesions that removal of all of the basal-cell nevi would be impractical. Frequent examination may be needed to detect early malignant change in any lesion.

Treatment of a single basal-cell cancer resulting from a basal-cell nevus can be accomplished by any of the conventional means. The problem cases are those with multiple rodent ulcers about the nose or eyelids. In these, surgical methods, including chemosurgery, should be used in preference to irradiation, since multiple rodent ulcers are to be treated and new cancers may be expected to develop over a period of many years. The use of irradiation would be unwise because of the resulting large areas of roentgen dermatitis. In far-advanced lesions the problem of therapy may be formidable, and it may require consultation and cooperation between the ophthalmologist, surgeon, radiation therapist, and dermatologist.

Summary and Conclusions

The basal-cell nevus is a relatively uncommon and infrequently recognized dysgenetic dermatosis. Reported cases of

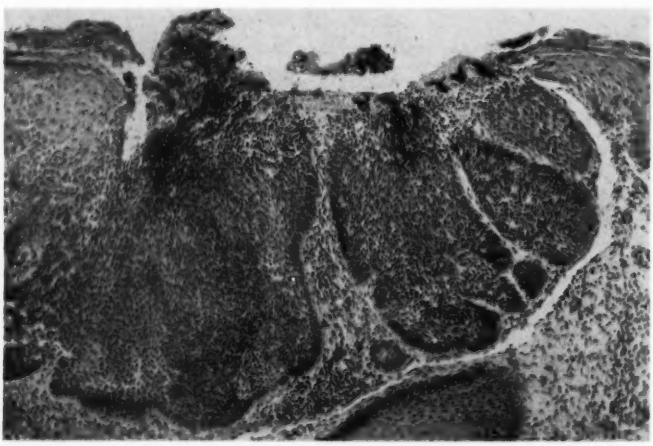

Fig. 6F (Case 1).—Section taken from small papule on the face, showing superficial ulceration of a superficially placed basal-cell epithelioma. The corium shows considerable senile elastosis and an inflammatory cellular infiltrate. Hematoxylin and eosin; reduced 40% from mag. × 160.

multiple basal-cell cancer associated with epithelioma adenoides cysticum should be reevaluated. It is possible that at least some of these patients may have had basal-cell nevi with a subsequent development of multiple cutaneous cancers.

Frequent associated anomalies of development include multiple dental follicular cysts of the mandible or maxilla, bifurcation of one or several ribs, milium-like bodies on the face, and epithelial cysts of the skin. Other defects of development are lipoma, fibroma of the ovary, congenital dorsal scoliosis, agenesis of the corpus callosum, and sometimes feeble-mindedness. These anomalies may represent a familial trait, and in each case one should investigate thoroughly the patient's pedigree.

The presenting complaints in patients with this syndrome may be caused by the cysts of the jaw or maxilla, although occasionally enlargement of a cutaneous lesion or its ulceration will cause the patient to seek medical attention. An important feature of this syndrome is the occurrence in young adults of multiple skin cancers developing from, or associated with, the basal-cell nevi. Emphasis must be placed on the danger of partial or complete destruction of the eyelids, eyes, and nose. To prevent destruction of these important structures, all basal-cell nevi found on the eyelids and nose should be completely removed.

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REFERENCES

1. Rodin, H. H.: Neurofibromatosis, A. M. A. Arch. Dermat. & Syph. 63:530 (April) 1951.

2. Carney, R. G.: Linear Unilateral Basal-Cell Nevus with Comedones, A. M. A. Arch. Dermat. & Syph. 65:471 (April) 1952.

3. Binkley, G. W., and Johnson, H. H., Jr.: Epithelioma Adenoides Cysticum: Basal-Cell Nevi, Agenesis of the Corpus Callosum and Dental Cysts, A. M. A. Arch Dermat. & Syph. 63:73 (Jan.) 1951.

4. Gross, P. P.: Epithelioma Adenoides Cysticum with Follicular Cysts of Maxilla and Mandible, J. Oral Surg. 11:160 (April) 1953.

5. Paul, N.: Cutaneous Neoplasms, London, H. K. Lewis & Co., Ltd., 1950, p. 46.

6. Nomland, R.: Multiple Basal Cell Epitheliomas Originating from Congenital Pigmented Basal Cell Nevi, Arch. Dermat. & Syph. 25:1002 (June) 1932.

7. Adamson, H. G.: Two Cases of Multiple Rodent Ulcer, with a Note on the Possible Relationship Between Multiple Rodent Ulcer and Epithelioma Adenoides Cysticum of Brooke, Lancet 2:1133, 1908.

8. Jarisch, A.: Zur Lehre von den Hautgeschwulsten, Arch. Dermat. u. Syph. 28:163, 1894.

9. White, J. C.: Multiple Benign Cystic-Epithelioma, J. Cut. & Genito-Urin. Dis. 12:477, 1894.

10. Stelwagon, H. W., and Gaskill, H. K.: Treatise on Diseases of the Skin, Ed. 9, Philadelphia, W. B. Saunders Company, 1921, p. 681.

11. Pautrier, L. M., and Archambault, G.: Extraordinary Case of Cutaneous Epitheliomatosis: More than 200 Epitheliomata Appearing over 23 Years on the Entire Skin, Without Metastases, and Showing 5 Histologic Variations, Bull. Assoc. franç. étude cancer 16:835 (Dec.) 1927.

12. Little, E. G. G.: A Note on 2 Cases of Epithelioma Adenoides Cysticum (Brooke) Tricho-Epithelioma Papulosum Rodens (Jarisch), Brit. J. Dermat. 26:173 (May) 1914.

13. Ormsby, O. S.: Case: Multiple Epitheliomas, Arch. Dermat. & Syph. 21:667 (April) 1930.

14. Nisbit, T. W.: Multiple Basal-Cell Epitheliomas Originating from Congenital Pigmented Basal Cell Nevi, Arch. Dermat. & Syph. 47:373 (March) 1943.

15. Mueller, H. M.: Case presented to Chicago Dermatological Society, March 20, 1957.

ABSTRACT OF DISCUSSION

DR. SAMUEL M. BLUEFARB, Chicago: Dr. Howell and Dr. Caro should be congratulated on this presentation which offers another link in the morphologic variants of these cutaneous diseases which result from a congenital defect. Basal-cell nevus should probably be evaluated according to its interrelationships with the broad group of nevoid disorders, particularly multiple benign cystic epithelioma, syringomas, epiloia, Sturge-Weber syndrome, neurofibromatosis, epithelioma adenoides cysticum, fibroepithelioma of Pinkus, and the various hamartomas. Brinkley's case was reminiscent of epiloia and Rodin's case of neurofibromatosis. All of these syndromes have characteristic features in common: They are hereditary, have clinical features which are interrelated, occur or become active at puberty, and arise from nests of embryonal cells. In addition, there may be associated involvement of the osseous or nervous system.

In my opinion, the common hereditary features should be emphasized in all cases and the genetic

background should be investigated. Although this condition has been mentioned in dermatologic literature, its association with other embryological errors has not previously been stressed. The relationship to anomalies in development have been properly stressed in this report.

The relationship of basal-cell nevus to trichoepithelioma and fibroepithelioma of Pinkus is of great interest. It is possible that many cases which have been designated "trichoepithelioma" with associated skin malignancies were actually basal-cell nevi. The relationship between epithelioma adenoides cysticum, trichoepithelioma, and basal-cell epithelioma were discussed previously by Traenkle. Pinkus, in 1953, described four cases of "Premalignant Fibroepithelial Tumors of the Skin" in which he considered them as an unusal variety of basal-cell epithelioma. Rodin's case both from the clinical and histologic aspects could be compatible with this diagnosis.

The relationship of basal-cell nevus to multiple cutaneous cancers was also stressed in this report. It has been found that this type of carcinoma is only malignant locally and does not show generalized metastases. However, the destruction and disfigurement resulting from these lesions makes immediate and total therapy imperative. This may not be possible in all cases, since a specific diagnosis cannot always be made by histologic examination. The difficulties encountered in differentiating such closely related conditions as epithelioma adenoides cysticum and basal-cell nevus was discussed by Lund in his monograph, "Tumors of the Skin."

I certainly agree that early definitive and prophylactic therapy is essential. Because of a predilection for the eyelids, malignant degeneration frequently occurs in this area. Therefore, the most practical approach to this problem is complete removal of all lesions on the face.

The authors are to be congratulated in offering a comprehensive presentation of another link in the dysgenetic dermatoses and their relationship to multiple cutaneous carcinomas and association with anomalies of development.

Dr. Frances A. Ellis, Baltimore: I had an opportunity to read this paper, and I enjoyed the presentation very much.

As to nomenclature, the use of the word "nevus" here may be questioned. I find, in talking to undergraduate medical students and even postgraduate students in dermatology, that if you ask them for a definition of "nevus" they will usually give you the pathologist's definition, that is, a tumor containing nevus cells. If that is the true and only definition for a nevus, then much of dermatologic literature is incorrect and the dictionaries are wrong. Fortunately, most of us do not agree with that definition. The dermatologist usually uses the word nevus to mean a congentital abnormal (usually localized) growth of cells which are present at birth or their anlage is present at birth. The word in this presentation, "nevus," might need to be defined more accurately. Can we prove that these nevoid basal-cell tumors are different from other basal-cell epitheliomas?

We may try to do this by showing that they appear at an early age and by a genetic history, but is that sufficient? We do not know really what causes basal-cell epitheliomas in the first place.

In these cases, prophylactic measures are very important, even though you cannot remove all of the lesions. These patients must be observed frequently for possible progression of the lesions about the face and especially about the eyes. I had one man with innumerable lesions, mostly on the torso. At the age of 40, he developed one tumor the size of a fist before he had anything done about it. Fortunately, local excision was sufficient.

Dr. George H. Curtis, Cleveland: I am very much interested in Dr. Howell's and Dr. Caro's paper, because heretofore I had not been familiar with this syndrome, but six weeks ago a young man was sent to me as a case of multiple epitheliomatosis of the basal-cell type. He was 21 and gave the history that both his father and his grandfather were afflicted with this condition and his father had lost a good part of his upper lip because of it. The histologic picture, of course, ruled out all the other clinically similar conditions.

I should like to ask the question, shall we continue throughout these people's lives to remove these lesions from the face, particularly(?)—because this boy has been seen by four or five dermatologists, who have treated the condition by electrocoagulation, cautery, radium, and x-ray, and his face is considerably disfigured with scars.

Dr. Hamilton Montgomery, Rochester, Minn.: In regard to this whole problem, I think that it is important, as Dr. Howell and Dr. Caro have emphasized, that we keep classifying and subclassifying these conditions until we know more about the fundamental etiology of basal-cell cancer or its subdivisions or whether some types may be called nevoid disturbances or hamartoma.

On the other hand, at the Clinic, we are having so many atypical so-called adnexal tumors that it is hard to describe all of the classifications and subclassifications; also, as was mentioned by Dr. Bluefarb, there is a relation to fibroepithelial tumors, which some of these pictures resemble somewhat histologically. Herbert Lund had a great deal of difficulty in classification of tumors of the skin. He sent his original monograph or fascicle to several other people for criticism. I think he has done an excellent job.

A few years ago I can remember a paper of Dr. Marcus Caro on morphea-like epithelioma of both basal-cell type and squamous-cell type. I think he was perfectly right and the discussers were entirely wrong. I have enjoyed this presentation very much.

Dr. Herbert S. Alden, Atlanta: I recall observing three persons with this type of lesion. All three of them have been under observation for a period of from 5 to 10 years, during which time I have alternated between the diagnosis of acanthoma, epithelioma, and some other tumor, possibly a nevus. They have had numerous tumors removed with all kinds of methods.

One of these persons is very much scarred and has several areas of radiodermatitis from the use of x-ray. I therefore resorted to the use of liquid nitrogen on the smaller tumors. In the last two or three years, on all three of these patients, I have used liquid nitrogen entirely. I think this method turns out to be the best nonscarring treatment for this type of lesion. This treatment, of course, is not applicable around the eyelids.

Dr. Marcus R. Caro, Chicago: We wish to thank the discussers for their remarks and also for their questions, which brought up a few facets that are discussed in the paper but which could not be covered in the presentation.

It is now about 25 years since Nomland first used the term "basal-cell nevus," and yet it has not been easy to sell the idea that it is possible to have nevi composed entirely of basal cells, even though there is a precedent that should have made this concept readily acceptable. We know, for example, that the epidermis may give rise to malignant tumors of a special nature: squamous-cell cancer from the prickle cells and basal-cell cancer from the basal cells or the adnexa. Why, then, no basal-cell nevi?

Dr. Ellis brought up the question of the definition of nevi, and I think that this is an important source of confusion. To me, a dermatologic nevus is a congenital abnormality of development of any component of the skin, generally producing a hyperplasia. More than one tissue may be involved to produce pigmented hairy nevi of any other combination; or a single tissue may be involved, to result in nevi of nevus cells, hairs, sebaceous glands, sweat glands, blood vessels, lymphatics, and so on, or, as was mentioned this morning by Dr. Montgomery, the rare nevi of smooth muscle. Why, then, is it difficult to accept the possibility that nevi may result from a hyperplasia of basal cells alone?

The great difficulty in these cases has been posed by the wide discrepancy between the histologic features of the section and the gross appearance of the lesion, as well as the clinical course of the patient. In every patient presented today, the biopsy section was diagnosed by competent pathologists as a basal-cell cancer. This was true of the cases studied by Dr. Howell, and it was true of the patient whom I had the privilege of observing for the past eight years.

When I first saw this patient of Dr. Rodin at the Chicago Dermatological Society eight years ago, where she was presented as a case of neurofibromatosis, I obtained two biopsy specimens and prepared the sections which were presented to you on the screen today. Both sections were submitted to competent pathologists, and both were uniformly diagnosed as basal-cell cancer.

About one month ago I performed biopsies on five lesions from this same patient and again submitted sections from all to competent pathologists, and the histopathologic diagnosis again was uniformly basal-cell cancer. That is the point we wish to stress. It is important that this entity be brought to the attention not only of the dermatologists, most of whom are familiar with it, but particularly also of pathologists. General pathologists in studying these sections invariably make a histopathologic diagnosis of basal-cell cancer, and, as a result, some of these patients may be subjected to unnecessary mutilating operations. These lesions remain benign for many years, and only those on the face, particularly about the eyelids, nose, and nasolabial fold, tend to become more active, to invade, to ulcerate, and to become destructive.

The question was asked as to whether or not these lesions should be treated and what should be done. It is our feeling that, if possible, all of them should be removed as a prophylactic measure. While those on the trunk may never become malignant, one never knows, if the patient lives long enough, whether or not malignant supervention may not eventually take place. Certainly, all lesions on the face, particularly those about the eyes and nose, should be removed and removed as completely and as early as possible. What method of removal is used is of very little importance, because only local destruction is necessary. I would urge strongly that, if the lesions are still benign clinically, no irradiation of any type be used. I think that more damage is done in these cases by the use of x-rays or radium than is warranted. Remember, you are dealing with lesions which are going to be enlarging locally and which are going to become more numerous. If you produce a radiodermatitis in treating one lesion, you will certainly in time have other lesions developing within areas of radiodermatitis.

If the lesions are few, they can be destroyed by liquid nitrogen or by electrosurgical procedures. Almost any method can be used, but the important thing is to use some form of treatment which in

itself will not lead to unnecessary scarring. Dermabrasion has been used in some of these patients, and, if many lesions are present in a small area of skin, dermabrasion might well be the most feasible method. In the case of the little girl I presented, however, it should be very simple, with the patient under general anesthesia, to remove all the lesions by cutting them off with scissors and destroying the base with the actual cautery. By this method, most of her skin which is normal will be left intact and only the sessile or pedunculated base of the individual lesions will be destroyed.

In reply to the questions that were asked about differential diagnosis, these lesions are certainly nevoid because they are congenital abnormalities. How they are related to other congenital abnormalities of the skin is of very little consequence. It is important, however, to delineate these cases from those of other congenital abnormalities, such as multiple benign cystic epithelioma and the premalignant fibroepithelioma of Pinkus, and that can readily be done on histopathological grounds.

Pathology of the Dermatitis Produced by the Urticating Caterpillar, Automeris Io

DAVID L. JONES, M.D., and JOSEPH H. MILLER, Ph.D., New Orleans

Introduction

The order Lepidoptera contains many species of urticating caterpillars that can produce lesions in man. The more commonly known species in this country include the puss caterpillar (Megalopyge opercularis), the flannel moths (Megalopyge crispata and M. pyxidfera), the saddleback caterpillar (Sibine stimulea), the brown-tail moth (Euproctis phaeorrhoea), and the Io moth larva (Automeris io).

The puss and Io moth caterpillars are very common in the states bordering the Gulf of Mexico. Many cases of dermatitis from their venom occur each season. Bishopp [1] describes an epidemic of thousands of cases in Texas due to Megalopyge opercularis. In one city the schools were ordered closed until shade trees in the vicinities could be sprayed to destroy the caterpillars.

Beyer [2] described the signs and symptoms of contact venenation from the puss caterpillar which he experienced personally. There was immediate burning of the hand which proceeded rapidly to numbness and pain of the entire shoulder. Nausea and severe restlessness were also experienced. The severe pain persisted for seven hours despite 20 grains (1.3 gm.) of acetylsalicylic acid. The next day the skin in the axilla was drawn and tense. The lymph nodes were not enlarged. Lucas [3] described similar symptoms in cases of puss caterpillar venenation, with the addition of muscle cramps and extreme anxiety. Micks [4] reported 18 cases of puss caterpillar urtication. Eight of these cases presented a severe clinical picture, with acute stabbing pain extending rapidly from the contact site on an extremity to the trunk.

Lucas [3] found morphine, codeine, and epinephrine to be the best symptomatic therapy. Randel and Doan [5] also report good analgesia with codeine but diphenhydramine hydrochloride (Benadryl Hydrochloride) and tetracaine ointment were of no value.

Tyzzer [6] demonstrated the lesion produced by contact with the brown-tail moth larva. He reported that the nettling hairs penetrated the epidermis, acting as foreign bodies as well as injecting an irritating substance into the skin. The lesion was described as a necrosis of the epidermis around a nettling hair with a microscopic vesicle in the epidermis and inflammatory changes around the vessels in the corium.

Foot [7] described the pathology which resulted from contact with the puss caterpillar. He reported local necrosis and vesicle formation of the epidermis. The cellular reaction was mainly lymphocytic. There was an immediate burning sensation which lasted one-half to five hours. This was followed by the appearance of small vesicles which persisted for 48 to 72 hours.

Gundersen et al.,[8] Dreyer,[9] and Corkey [10] reported cases of ophthalmia nodosa due to the urticating hairs of caterpillars. A granulomatous foreign-body reaction was elicited by intraocular migration of the hairs. Enucleation was necessary in two cases.

No reports of clinical or pathological studies have been found concerning the lesion produced by the Io moth larva (A. io). The symptomatology is less severe

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Department of Medicine (Dr. Jones) and the Department of Microbiology (Dr. Miller), Louisiana State University School of Medicine.

and of shorter duration than that produced by contact with the puss caterpillar. Cases of venenation by the Io moth larva therefore probably do not often come to the attention of the physician. A heavy infestation of A. io on the grounds of a housing project in New Orleans prompted this investigation.

Materials and Methods

Numerous larvae of the Io moth were found in low-growing crepe myrtle trees from October to the first week in December. With the onset of colder weather, at this time, they began to spin cocoons.

The larvae which were collected ranged from 1 to 6 cm. in length. The entire larva, including the hairs, was a vivid light green color with a sublateral pair of parallel maroon and white stripes. There were six transverse rows of dorsal and lateral papillae, evenly distributed along the length of the larva. Several long urticating and nonurticating hairs extended from each papilla.

The inner surface of the ears of 6-week-old litter mate rats were stroked six times with a live caterpillar. Care was taken to insure contact with the urticating hairs. Gross observation and biopsies of the ears were done at intervals of 5, 15, and 30 minutes and 1, 2, 3, 6, 12, and 24 hours. A control biopsy was also performed. Sections were prepared and stained with hematoxylin and eosin. Cross sections of caterpillars were also studied.

Results

There was an immediate erythematous reaction at the site of contact. A pitting edema developed rapidly and was present grossly in five minutes. This represented the maximum visible response. In six hours the normal gross appearance of the ear was restored. No vesicle or areas of necrosis developed.

Microscopically there was marked edema of the corium and subcutaneous tissue with associated dilatation of the blood vessels.

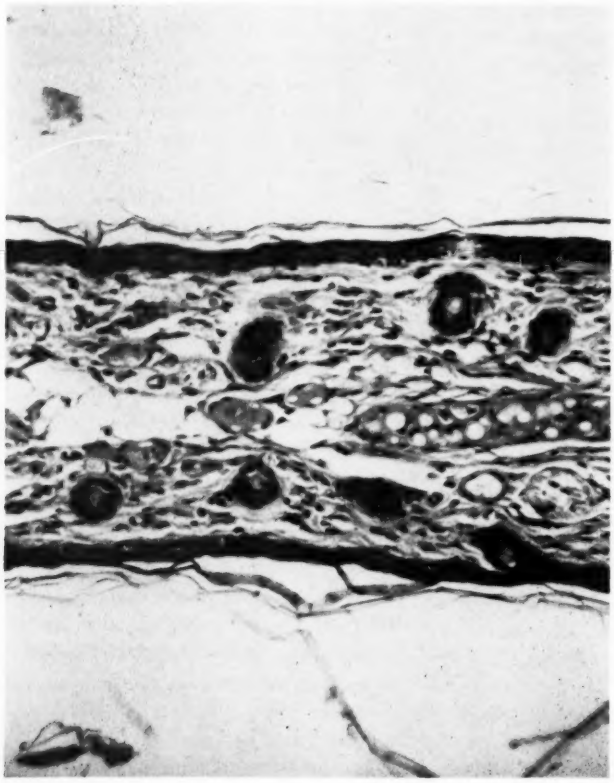

Fig. 1.—Cross section of rat ear. Normal control. All photographs were made at the initial magnification of ×100.

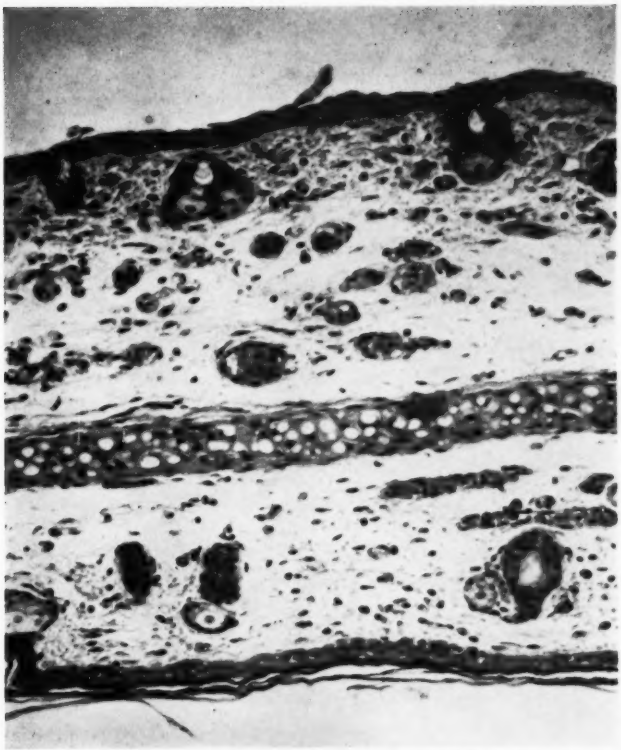

Fig. 2.—Cross section of rat ear five minutes after caterpillar contact. Section shows marked edema of corium and subcutaneous tissue, dilatation of blood vessels, and infiltration of polymorphonuclear leukocytes and macrophages.

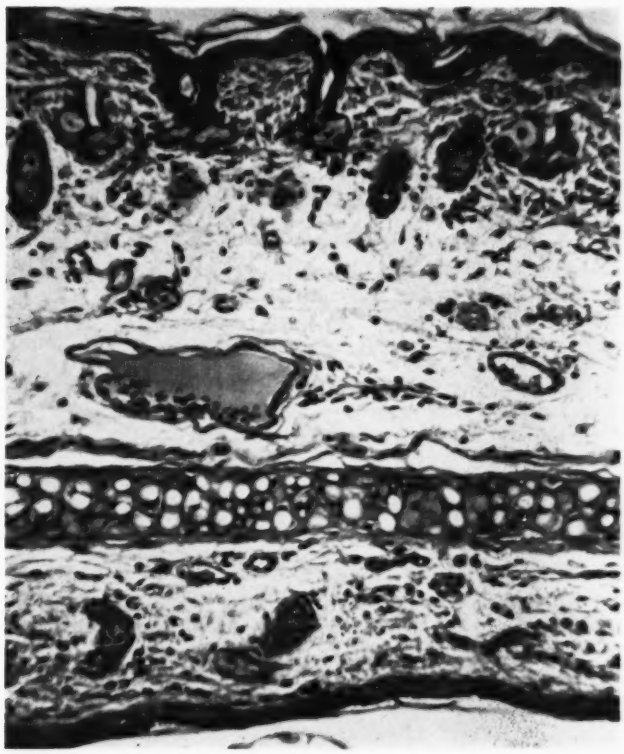

Fig. 3.—Cross section of rat ear at one hour after caterpillar contact. Section shows continued response.

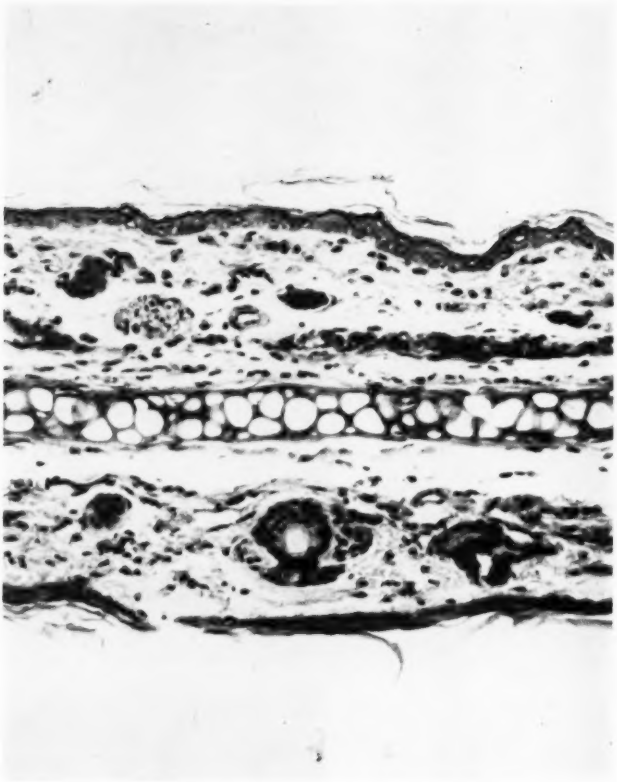

Fig. 4.—Cross section of rat ear at 12 hours. Compare with control.

There was a cellular response consisting of infiltration by polymorphonuclear leukocytes and macrophages. No unusual number of eosinophils was seen. The response was marked in the biopsy specimen taken five minutes after contact and remained apparent in subsequent biopsy specimens through the six-hour specimen.

The 12- and 24-hour biopsy specimens were normal. No areas of necrosis were seen, and no urticating hairs were found (Figs. 1-4).

The poison apparatus of the caterpillar consisted of urticating hairs mounted on a papilla. The urticating hair shaft was lined by a continuous thin hypodermis and had a plug-like tip and a diaphragm at the base which led to the poison gland.

Comment

The lesion produced by contact with the lo moth larva is an immediate erythematous wheal with rapid edema formation of the corium and subcutaneous tissue. The reaction lasts approximately six hours, and the affected area is normal grossly and microscopically after that time. In contrast to previously described lesions produced by other urticating caterpillars, there was no necrosis, vesicle formation, or hairs producing foreign-body reactions.

Randel and Doan[5] reported an 8% to 22% eosinophilia in cases of dermatitis produced by contact with Megalopyge lanata in Panama. This increase occurred immediately and decreased greatly on the second day. Sections of lesions produced

by contact with A. io did not show a local increase in eosinophils.

No attempt was made to investigate the composition or mechanism of action of the irritating substance. However, Tyzzer[6] found that the venom of the brown-tail moth larva was destroyed by dilute alkalies or heating to 115 C, and that it lysed red blood cells. D'Ingianni,[11] however, repeatedly failed to produce hemolysis but did not mention the species used in his study.

Valle et al.[12] made crude aqueous extracts of the venenating setae of Dirphia sp. and Megalopyge sp. They demonstrated a histamine content of Dirphia sp. extracts equal to a 0.02%-0.04% solution. The histamine content of the extracts of setae of Megalopyge sp. was found to be much lower. Acetylcholine was undetected in both species. It was concluded that the extracts also contained other active pharmacologic substances probably of a protein nature. The lesion produced by A. io is compatible, at least in part, with a substance containing histamine or one causing its release.

The "spine type" of venenating structure of Automeris io is similar to that of Megalopyge opercularis as described by Foot,[7] except that the glandular portion is located in the papillae and does not form a base about the venenating hairs.

Summary

The pathology of the dermatitis of the caterpillar of Automeris io is a rapidly developing edema of the corium and subcutaneous tissue without necrosis. The reaction is of approximately six hours' duration.

The urticating substance was not analyzed. On clinical evidence, however, the reaction is compatible with one caused, at least in part, by histamine or a histamine release phenomenon.

The poison apparatus of the caterpillar consists of venating hairs mounted on papillae. Each hair shaft is open to a poison gland in the papilla.

School of Medicine, Louisiana State University.

Dr. Monroe Samuels, Assistant Director of Pathology, Charity Hospital of Louisiana, assisted in the microscopic interpretation of the biopsy specimens.

REFERENCES

1. Bishopp, F. C.: The Puss Catepillar and the Effects of its Sting on Man, U. S. Department of Agriculture Circular 288, 1923.

2. Beyer, G. E.: Urticating and Poisonous Caterpillars, Quart. Bull. Louisiana Board Health 13:161, 1922.

3. Lucas, T. L.: Poisoning by Megalopyge Opercularis (Puss Caterpillar), J. A. M. A. 119: 877 (July 11) 1942.

4. Micks, D. W.: Clinical Effects of the Sting of the Puss Caterpillar (Megalopyge Opercularis) on Man, Texas Rep. Biol. & Med. 10:399, 1952.

5. Randel, H. W., and Doan, G. B.: Caterpillar Urticaria in the Panama Canal Zone: Report of Five Cases, in Venoms, A. A. A. S. publication No. 44, Washington, D. C., 1956.

6. Tyzzer, E. E.: The Pathology of the Brown-Tail Dermatitis, J. M. Res. 16:43, 1907.

7. Foot, N. C.: Pathology of the Dermatitis Caused by Megalopyge Opercularis, a Texan Caterpillar, J. Exper. Med. 35:737, 1922.

8. Gundersen, T.; Heath, P., and Garron, L. K.: Ophthalmia Nodosa, Tr. Am. Ophth. Soc. 48:151, 1950.

9. Dreyer, V.: Ophthalmia Nodosa, Acta ophth. 31:429, 1953.

10. Corkey, J. A.: Ophthalmia Nodosa Due to Caterpillar Hairs, Brit. J. Ophth. 39:301, 1955.

11. D'Ingianni, V.: Urticaria Produced by Poisonous Caterpillars, New Orleans M. & S. J. 96:356, 1944.

12. Valle, J. R.; Picarelli, Z. P., and Prado, J. L.: Histamine Content and Pharmacological Properties of Crude Extracts from Setae of Urticating Caterpillars, Arch. internat. pharmacodyn. 98:324, 1954.

Influence of Specific Antibody on Herpes Simplex Infections in Tissue Culture

CLAYTON E. WHEELER, M.D., and CHARLES M. CANBY, M.S., Charlottesville, Va.

Persons who suffer from recurrent herpes simplex infections have neutralizing or complement-fixing antibodies to herpes simplex virus in their sera, usually in high titer.[4,6-9,11-16,18-20] The antibody level in the sera of these patients, according to available evidence,[6,9,11-16,19] does not fluctuate in response to the recurrent infection. (The anibody level is as high before the recurrence as it is during or after.) These observations suggest that a high level of specific antibody in the serum is incapable of eradicating the herpes virus even though it may limit its spread.

The influence of specific antibody upon the course of experimental herpes infections in tissue cultures has been studied by two groups of investigators. Andrewes [3] showed that herpes simplex infections could develop in tissue cultures in the presence of specific antibody providing the virus was added one-half hour before the addition of the antibody. Black and Melnick [5] enlarged upon this work, using the herpes B virus (a relative of the herpes simplex virus) whose natural host is the monkey, in monkey-kidney tissue cultures. They added tissue culture medium containing antibody to herpes B virus to the cultures at varying intervals after the addition of herpes B virus and observed the influence of the antibody upon the course of the infection. In the absence of antibody the infection spread rapidly throughout the cultures. When specific antibody was present the infection remained localized to plaques and spread of the infection occurred by enlargement of the peripheral portion of the plaques instead of by wide dissemination through the fluid culture medium. Their experiments were restricted to short-term effects under conditions of limited cell growth and multiplication because of the cell type and the culture medium which they employed.

In order to study further the effect of specific antibody upon the course of the herpetic infection, HeLa cultures infected with herpes simplex virus were employed as models in our laboratory. After establishment of the herpes infection some of the cultures were nourished with growth medium containing no demonstrable specific antibody and others were nourished with growth medium containing large amounts of specific antibody. Cultures nourished with medium containing no antibody were rapidly destroyed by the virus. Cultures nourished with medium containing specific antibody survived; the cells multiplied, and an apparently endless number of serial subcultures could be made, but these cultures continued to be infected with the herpes simplex virus.

Materials and Methods

A. Cells and Culture Media.—HeLa cells which had been passed serially in our laboratory were grown in 16×125 mm. screw-capped culture tubes kept in stationary slant racks at 35 C. The growth medium (GM) used in most of the work consisted of 40% human serum, 5% chick-embryo extract, and 55% balanced salt solution (Hank's). A

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From the Departments of Dermatology and Microbiology, University of Virginia Department of Medicine Associate Professor of Dermatology (Dr. Wheeler) and Research Assistant (Mr. Canby).

small number of cultures were nourished with 40% human serum in Eagle's basal medium.[10] The methods used in the preparation of the cultures and growth medium have been described in detail elsewhere.[21,22]

B. Virus Strains.—Three strains of herpes simplex virus were used: (1) HF, which was obtained from the American Type Culture Collection; (2) ST, from a recurrent herpes lesion on the thigh of a 23-year-old woman, and (3) CR, from recurrent herpes lesions on the face of a 6-year-old girl.[23] The stock virus which was used to inoculate HeLa cultures had been passed 5 to 12 times in HeLa cells kept in 10% horse-serum maintenance solution (HSMS).

C. Establishment of High Antibody and No Antibody Serum Pools.—Serum was obtained from volunteer medical students and tested for the presence of neutralizing antibody as follows: Equal volumes of undiluted inactivated serum* were added to serial tenfold dilutions of herpes simplex virus in HSMS. The virus-serum (and virus-HSMS control) mixtures were rotated in a revolving drum at 35 C for one-half hour and then added to cultures of HeLa cells (two to three cultures per dilution to be tested) which had been washed twice with 2 ml. of Hank's balanced salt solution (BSS). After incubation of these cultures in slant racks at 35 C for one hour, 1 ml. of HSMS was added and the cultures were reincubated at 35 C. The number of plaques of herpes-infected cells in the cultures were counted at 48 hours for ST virus and at 72 hours for HF and CR viruses. The number of infectious units of virus contained in the virus-serum (or virus-HSMS) mixture was then calculated as described below.

Approximately 50% of the sera tested contained no demonstrable neutralizing antibody (dilutions of virus containing 4 to 60 infectious units produced as many plaques after incubation with the test serum as after incubation with the control HSMS). Approximately 50% of the sera neutralized varying amounts of herpes simplex virus. Sera with small amounts of neutralizing antibody were discarded, and sera containing large amounts of neutralizing antibody were saved. Sera of five to seven donors which showed no demonstrable neutralizing antibody were pooled, and this serum pool was used to prepare the growth medium (GM) described above. Similarly, sera of five to seven donors which contained large amounts of antibody were pooled and this serum pool was used to prepare GM. The completed XABGM was tested and found to contain no demonstrable neutralizing antibody, and the completed HABGM was found to contain enough antibody in 0.1 ml. to neutralize all except 20 to 30 infectious units of virus when incubated with an equal volume of virus suspension containing 20,000 to 30,000 infectious units.

D. Method Used in the Titration of Virus.—Virus titers were determined by a method which has been described elsewhere.[22] The method consisted essentially of the preparation of serial tenfold dilutions of the virus sample to be tested. Aliquots of these dilutions were added to HeLa cultures which were incubated for 48 to 72 hours,† at which time herpes plaques were counted at the dilution at which the largest number of countable plaques, usually 20 to 80, were found. Since one herpes plaque was initiated by a single infectious unit of virus, the virus titer expressed in infectious units per milliliter could be calculated from the formula $n=y/vx$ when n equals the number of infectious units of virus present per milliliter, y equals the average number of plaques counted, v equals the volume of the sample in milliliter, and x equals the dilution of the sample on which the plaque counts were done.

E. Preparation and Maintenance of Herpes Infected Cultures Used in Studying Effect of Antibody upon Course of Infection.—HeLa cultures consisting of approximately 300,000 cells arranged in monolayer sheets were washed twice with 2 ml. of BSS after decanting the original GM. Varying amounts of virus (1 to 1000 tissue-culture infectious units) were added to the cultures and time (one to five hours) was allowed for virus to attach to cells. NABGM or HABGM was then added to the cultures. The cultures were observed daily for herpetic cytopathogenesis and an estimate made of the relative proportion of infected and uninfected cells. The culture medium was changed daily for the first two or three weeks after infection and thereafter only when the pH became too acid (every second or third day). After removal of medium from the cultures, it was stored in the CO_2 box (—45 C) or the deep freeze (—20 C) and later titrated for virus. In some instances the medium was centrifuged before storage and the supernatant portion of the medium stored separately from the sediment.

Subcultures were performed by scraping the cells off the wall of one culture tube and adding 3 ml. of fresh medium. The cells and medium were forced up and down 8 or 10 times in a 5 ml. pipette, and 1 ml. of this cell suspension was added

*Inactivation of the serum was carried out by incubation in a water bath at 56 C for one-half hour. Fresh sera which were not treated in this manner inactivated small amounts of herpes simplex virus, although they contained no demonstrable specific antibody.

†With ST virus, plaque counts were done at 48 hours. Plaque counts were done at 72 hours with CR and HF viruses because plaques were formed more slowly with these strains of virus and counts were slightly more accurate at 72 hours than at 48 hours.

to each of three fresh culture tubes. Thus, at each subculture the cells (and virus in the infected cultures) were diluted by a factor of 3.

Results

Uninfected, control HeLa cultures were prepared and maintained in parallel with each group of infected cultures. The control cultures nourished with NABGM and HABGM showed a gradual increase in thickness of the cell sheet until the thicker, triangular center portion sloughed away from the glass culture tube, leaving only a V-shaped border of cells adherent to the glass. Cells gradually regrew in the bare central area, only to slough again if the cultures were kept long enough for the cell sheet to become thick again. The cells of older cultures frequently became granular and stringy, and localized areas of the cell sheet peeled away from the glass, producing a "swiss cheese" appearance. However, the cells in these old cultures were capable of rapid growth and multiplication upon subculture and they could be serially subcultured in NABGM and HABGM indefinitely (20 subcultures with no suggestion of limitation of cell growth or multiplication).

Eighty-two cultures were inoculated with herpes simplex virus (thirty-five with ST, thirty-five with HF, and twelve with CR) and nourished with HABGM. Sixty-eight infected cultures (thirty-eight with ST, twenty-five with HF, and five with CR) were nourished with NABGM. Since the effect was the same whether the ST, HF, or the CR strains of virus were used, the results of the experiment are presented in terms of the course of the herpes virus infection in the presence of the two different types of growth medium—HABGM and NABGM.

The herpetic infection in cultures nourished with NABGM (Fig. 1) spread relentlessly until the entire cell population was destroyed, which took place within 5 to 10 days after inoculation of the virus. Cultures inoculated with large amounts of virus (500 to 1000 infectious units) appeared to be destroyed more rapidly than cultures inoculated with small amounts of virus (1 to 200 infectious units). The influence of the amount of virus inoculated upon the course of the infection is under more detailed study at the present time in cultures nourished with either NABGM or HABGM. As would be expected, new virus appeared promptly in the medium of the NABGM cultures and high titers of virus (10^6 infectious units per milliliter) were attained. The virus titer in the medium increased as the infection spread and decreased as the cells were destroyed and were washed away with the daily changes of media.

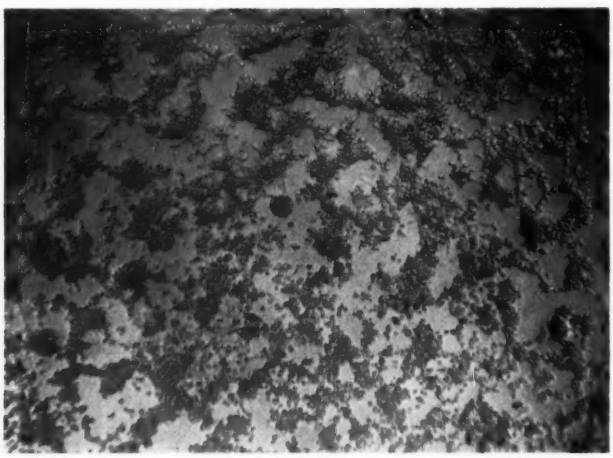

Fig. 1.—HeLa culture nourished with NABGM. Five days after inoculation of 80 infectious units of ST herpes simplex virus. Almost every cell is infected.

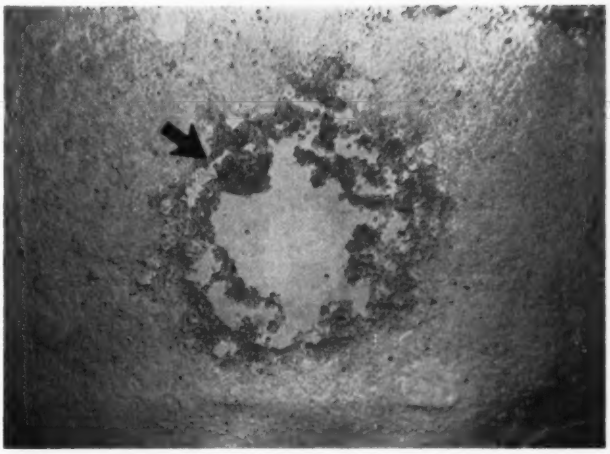

Fig. 2.—HeLa culture nourished with HABGM. Five days after inoculation of 80 infectious units of ST herpes simplex virus. The herpes infection is limited to plaques (arrow), and the majority of the HeLa cells are still uninfected.

The course of the herpetic infection in cultures nourished with HABGM will now be described. Cultures inoculated with large amounts of virus (500 to 1000 infectious units) developed widespread cytopathogenesis, but there always remained a few uninfected cells from which the cultures regrew into monolayer sheets of "normal" cells which were bespattered with small groups of infected cells. Cultures inoculated with small amounts of virus (1 to 200 infectious units) developed discrete plaques of herpes-infected cells (Fig. 2). These plaques enlarged at the periphery until they became confluent and large areas of the culture were affected. At times infected cells or clumps of cells dropped off the glass and lodged at distant sites adjacent to uninfected cells and initiated new plaques of infection. As the plaques of infected cells enlarged and the infected cells dropped off the glass, new, apparently uninfected, cells grew into these areas and later became infected. A shifting pattern of infection and regrowth which persisted indefinitely (as long as eight months in one instance) without evidence of cure of the infection or death of the cultures was thus established.

Infected cultures nourished with HABGM were subcultured as described under Materials and Methods. The day after subculture both "normal"-appearing and infected cells could be seen scattered over the glass surface of the culture tube. In the ensuing four to seven days, depending upon the number of cells in the inoculum at subculture, the "normal" cells multiplied to form islands which coalesced to form sheets of cells. The infected cells were seen at the periphery of the growing islands of morphologically uninfected cells, and when the islands coalesced to form sheets the infected cells formed an outline of the preceding islands. When sheets of cells were formed, the infected cell foci began to spread and in a few days large areas of the cell sheet had become infected and dropped off the glass. "Normal" cells still could be seen, however, and regrowth again took place in the areas destroyed by infection.

Subculture of infected cultures nourished with HABGM can apparently be performed indefinitely. One set of cultures infected with ST virus has been subcultured 16 times over a period of four and one-half months with no evidence of loss of virus or loss of the cultures. Sixteen subcultures implies dilution of the original material by a factor of over 150,000,000. Since the original culture contained 300,000 cells and 20 infectious units of virus and the 16th passage culture contained approximately the same number of cells and over 200,000 infectious units of virus, it is evident that multiplication of cells and virus occurred.

Evidence that HABGM cultures have persistently carried virus has been derived from three observations. First, the cultures have consistently shown evidence of herpetic cytopathogenesis (giant cells, intranuclear inclusions, clumping, and round cells), in both stained (H & E) and unstained preparations. Second, the decanted medium has almost always been infectious for HeLa cells. Apparently the infectious component of the decanted culture medium has been associated with individual cells or cell clumps, since centrifugation of the decanted HABGM at 3000 rpm has removed all except a very occasional single infectious unit from the supernate and the sediment has contained 20 to 5000 infectious units of virus per milliliter. Third, switching HABGM cultures to NABGM has resulted in complete destruction of the cultures and the appearance of large amounts of virus in the culture medium (up to 6,000,000 infectious units of virus per milliliter). In each of the 16 subcultures of the example cited in the preceding paragraph virus was demonstrated by all three of these methods.

It is worth stressing that the infected HABGM cultures appear to be composed of two types of cells: (*a*) "normal"-appearing HeLa cells and (*b*) virus-infected cells which show typical changes of herpetic infection (Fig. 3). The virus-infected cells have the same microscopic characteristics as virus-infected cells grown or maintained in medium which contains no antibody, with one possible exception. In some of the HABGM cultures, especially those infected with HF virus, the infected cells seem to be clumped together in masses and individual cell outline is not as evident as in cultures containing no antibody (Fig. 4).

Comment

The presence of specific neutralizing antibody in the growth medium of herpes simplex-infected HeLa cultures under the conditions of this experiment created a relatively stable relationship between the virus and the cells of the cultures so that neither were the cultures destroyed by the virus nor was the virus eliminated from the cultures. These observations in some respects parallel those of Ackermann and Kurtz,[1,2] who infected HeLa cultures with poliomyelitis virus. As long as specific antibody against poliomyelitis virus was present in the growth medium, the cultures survived. The HeLa cells in the infected, or "carrier" cultures were different in microscopic appearance from the cells in uninfected HeLa cultures, but they multiplied and serial subcultures could be made. Withdrawal of specific antibody from the growth medium resulted in destruction of the cultures, and usually, but not always, this pro-

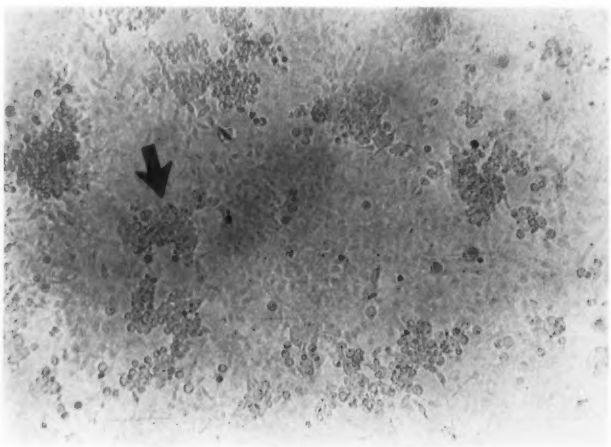

Fig. 3.—Tenth subculture of herpes simplex (ST strain)-infected "carrier" culture of HeLa cells nourished with HABGM. Note central area of normal-appearing cells. Arrow points to infected cells.

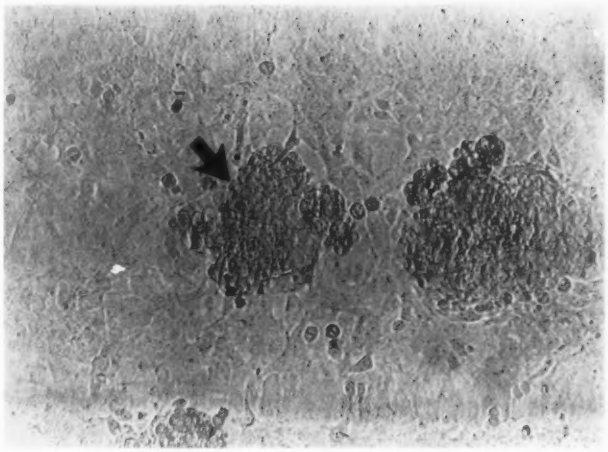

Fig. 4.—Third subculture of herpes simplex (HF strain)-infected "carrier" culture of HeLa cells nourished with HABGM. Arrow points to infected cells which have clumped together.

cedure was associated with the appearance of poliomyelitis virus in the culture medium. These observations prompted Ackermann and Kurtz to suggest that specific antibody, in addition to the usual functions of elimination of virus and limitation of its spread, may at times act in such a fashion as to preserve virus.

Herpes simplex-infected "carrier" cultures differed from poliomyelitis "carrier" cultures in at least two ways: 1. Herpes "carrier" cultures always presented islands and patches of morphologically uninfected, "normal"-appearing cells interspersed with infected cells. 2. Infectious herpes simplex virus could always be demonstrated in the "carrier" cultures.

Herpes simplex virus appears to spread in tissue cultures by at least three mechanisms: 1. Cell-to-medium-to-cell spread. Free virus is released by the infected cells into the fluid culture medium and spreads through this medium to cells at distant sites. This type of virus spread was apparently observed in the NABGM cultures, but it was not evident in the HABGM cultures. 2. Cell-to-cell spread. Virus spreads from an infected cell to an adjacent uninfected cell. It is not clear whether the virus in this instance spreads from cell to cell without entering the fluid medium or whether it travels through the fluid medium, even though this may be a very short distance. This type of spread is seen when no antibody is present in the medium, but it also occurs in the presence of specific antibody. At first glance this would appear to be evidence in support of cell-to-cell spread without entry of the virus into the fluid medium, but virus in a small area surrounding an infected cell might be in excess of available antibody at this localized area, and the spread might, therefore, still be through the medium. 3. Infected cells or small clumps of infected cells separate from the tissue culture sheets and travel through the medium to lodge at uninfected sites where new infectious foci are established. This method of spread occurs whether there is antibody in the medium or not. The spread of virus at the new focus must be similar to that outlined under Mechanism 2.

What effect does specific antibody have on the course of herpes simplex infections in man, and can any of the information obtained from the tissue culture model be applied to herpes infections in man? In the nonimmune person (primary herpes simplex infection) it seems likely that the herpes simplex virus spreads via the body fluids to cause widespread infection (skin, mucous membrane, blood, liver, gastrointestinal tract, brain, etc.) much as the infection becomes widespread in tissue cultures which contain no antibody. The presence of antibody in the body fluids (recurrent herpes

simplex infections) or tissue-culture fluids prevents dissemination of the virus, and the infection remains localized. The presence of specific antibody, even in large amounts, does not eradicate the virus in the tissue culture model or in man who has the recurrent form of the disease. Failure of antibody to eradicate intracellular virus might be expected if antibody cannot enter cells (or can enter cells only in small quantity) and if the virus can spread from cell to cell without entry into body fluids (or if localized areas or virus excess allow unneutralized virus to pass from cell to cell). Under these conditions the presence of antibody might conceivably contribute to the survival and persistence of the virus by helping to establish a balance between cell destruction and new cell formation. If such be the case it would seem unlikely that measures designated to raise antibody levels in patients with recurrent herpes simplex infections would be effective in eliminating the disease. It might also help to explain the establishment of new recurrent herpes lesions at sites of vaccination with live virus in the treatment of patients with recurrent herpes simplex infections.[17]

A pertinent question to which there is no available answer might be asked: Why does the recurrent herpes simplex lesion stop growing after it attains a certain size? If cell-to-cell spread occurs in the presence of antibody, why would the lesion not continue to spread as long as uninfected cells are available? The limiting factor in the spread of a local herpetic lesion may not be antibody alone. Cellular elements associated with inflammation and humoral elements other than specific antibody may be important. In this connection it may be pointed out that the individual herpes simplex vesicle on the skin or mucous membrane of the nonimmune person (primary herpes simplex infection) is essentially the same size as the vesicle which occurs in the immune person (recurrent herpes simplex infection), although more grouping of vesicles may occur in the immune person (localizing effect of antibody?).

One of the aims of this experiment was to see whether a latent or inapparent infection could be produced in tissue culture by growing herpes-infected HeLa cells in medium containing specific antibody. It was hoped that if such a model could be established some light could be shed upon the state of the herpes simplex virus in tissues in the interval between recurrences of this disease. Infected cultures kept at 35 C in medium containing antibody showed no tendency toward latent or inapparent infection, however, nor was there any indication that herpes-resistant cells developed in these cultures.

Conclusions

1. In HeLa-cell cultures which are infected with herpes simplex virus and nourished with growth medium containing no demonstrable neutralizing antibody the virus infection spreads relentlessly and destroys the cultures completely.

2. In HeLa-cell cultures which are infected with herpes simplex virus and nourished by growth medium containing large amounts of neutralizing antibody the virus infection persists but the cultures are not destroyed. Infected cultures can be passed serially, apparently indefinitely, without loss of the cultures or loss of the virus as long as specific neutralizing antibody is present.

3. Both in humans with recurrent herpes simplex and in the herpes-infected tissue culture model the presence of specific neutralizing antibody fails to eradicate the herpes simplex virus.

University of Virginia Hospital.

REFERENCES

1. Ackermann, W. W.: Mechanisms of Persistent and Masked Infections in Tissue Culture, Ann. New York Acad. Sc. 67:392 (April 19) 1957.

2. Ackermann, W. W., and Kurtz, H.: Observations Concerning a Persisting Infection of HeLa Cells with Poliomyelitis Virus, J. Exper. Med. 102:555 (Nov.) 1955.

3. Andrewes, C. H.: Tissue-Culture in the Study of Immunity to Herpes, J. Path. & Bact. 33:301, 1930.

4. Andrewes, C. H., and Carmichael, E. H.: A Note on the Presence of Antibodies to Herpes Virus in Post-Encephalitic and Other Human Sera, Lancet 1:857 (April 19) 1930.

5. Black, F. L., and Melnick, J. L.: Micro-Epidemiology of Poliomyelitis and Herpes-B Infections, J. Immunol. 74:236 (March) 1955.

6. Blank, H., and Rake, G.: Viral and Rickettsial Disease of the Skin, Eye and Mucous Membranes of Man, Boston, Little, Brown & Company, 1955, p. 63.

7. Burnet, F. M., and Lush, D.: Herpes Simplex; Studies on Antibody Content of Human Sera, Lancet 1:629 (March 18) 1939.

8. Burnet, F. M., and Williams, S. W.: Herpes Simplex: A New Point of View, M. J. Australia 1:637 (April 29) 1939.

9. Dudgeon, J. A.: A Complement Fixation Test for Herpes Simplex Infections, J. Clin. Path. 3:239 (Aug.) 1950.

10. Eagle, H.: The Specific Amino Acid Requirements of a Human Carcinoma Cell (Strain HeLa) in Tissue Culture, J. Exper. Med. 102:37 (July) 1955.

11. Frank, S. B.: Formalized Herpes Virus Therapy and the Neutralizing Substance in Herpes Simplex, J. Invest. Dermat. 1:267 (Aug.) 1938.

12. Gajdusek, D. C.; Robbins, M. L., and Robbins, F. C.: Diagnosis of Herpes Simplex Infections by the Complement Fixation Test, J. A. M. A. 149:235 (May 17) 1952.

13. Garabedian, G. A., and Syverton, J. T.: Studies on Herpes Simplex Virus: 1. An Antigenic Analysis of 4 Strains of Virus Isolated from a Human Subject, J. Infect. Dis. 96:1 (Jan.-Feb.) 1955.

14. Holzel, A.; Feldman, G. V.; Tobin, J. O., and Harper, J.: Herpes Simplex: A study of Complement Fixing Antibodies at Different Ages, Acta pædiat. 42:206 (May) 1953.

15. Jawetz, E.; Allende, M. F., and Coleman, V. R.: Studies on Herpes Simplex Virus: IV. The Level of Neutralizing Antibodies in Human Sera, J. Immunol. 68:655 (June) 1952.

16. Jawetz, E., Allende, M. F., and Coleman, V. R.: Studies on Herpes Simplex Virus: VI. Observations on Patients with Recurrent Herpetic Lesions Injected with Herpes Viruses or their Antigens, Am. J. M. Sc. 229:477 (May) 1955.

17. Lazar, M. P.: Vaccination for Recurrent Herpes Simplex Infection, A. M. A. Arch. Dermat. 73:70 (Jan.) 1956.

18. Nagler, F. P. O.: A Herpes Skin Test Reagent from Amniotic Fluid, Australian J. Exper. Biol. & M. Sc. 24:103 (June) 1946.

19. Scott, T. F. M.; Coriell, L.; Blank, H., and Burgoon, C. F.: Some Comments on Herpetic Infection in Children with Special Emphasis on Unusual Clinical Manifestations, J. Pediat. 41:835 (Dec.) 1952.

20. Stark, M. M.; Kibrick, S., and Weisberger, D.: Studies on Recurrent Aphthae: Evidence that Herpes Simplex is Not the Etiological Agent, with Further Observations on the Immune Responses in Herpetic Infections, J. Lab. & Clin. Med. 44:261 (Aug.) 1954.

21. Syverton, J. T.; Scherer, W. F., and Elwood, P. M.: Studies on the Propagation in Vitro of Poliomyelitis Viruses: V. The Application of Strain HeLa Human Epithelial Cells for Isolation and Typing, J. Lab. & Clin. Med. 43:286 (Feb.) 1954.

22. Wheeler, C. E.: The Effect of Temperature upon the Production of Herpes Simplex Virus in Tissue Culture, J. Immunol., to be published.

ABSTRACT OF DISCUSSION

Dr. Maurice Sullivan, Baltimore: In well-conceived and beautifully conducted experiments, Dr. Wheeler has demonstrated the following findings:

1. When HeLa-cell cultures were infected with herpes simplex virus and nourished with growth medium containing no demonstrable antibody, the virus infection spread relentlessly and completely destroyed all the cells in the culture.

2. By contrast, when large amounts of neutralizing antibody were added to the growth medium of HeLa-cell cultures infected with herpes simplex virus, the cultures were not destroyed, and it was possible to pass the cultures serially 16 times, without loss of cultures or virus as long as specific neutralizing antibody was present.

Now, let us examine these results to determine whether they are analogous to the clinical situation. Certainly, the complete destruction of the cultures, when no neutralizing antibody was added, is not comparable to the primary infection in man, because, in spite of an occasional severe initial attack in man, the infection is always limited. This probably means that locally some of the cells must receive an antigenic stimulus, which results from activity of viral antibody. The viral antibody very likely develops soon or immediately after the infection, as a result of virus liberated from damaged cells.

However, there are two other reasons why, clinically, the initial infection with herpes simplex is limited. First, it is not possible, except, perhaps, under extraordinary experimental conditions, to produce an overwhelming and widespread virus infection, that is, to deliver the virus to numerous cells over wide areas. Second cell populations

may be heterozygous, consisting of susceptible and resistant cells, and only the susceptible cells will accept the virus. The conditions in Wheeler's experiment were, therefore, not comparable to those in vivo, insofar as the initial infection is concerned. On the other hand, the chronic experimental infection produced by Wheeler was comparable in many respects to that in vivo. The addition of neutralizing antibody to the original growth medium and to the growth medium in the 16 subcultures apparently created an interference phenomenon, permitting a chronic carrier state similar to that in man.

Now, this is a feat of considerable importance, as it has provided investigators with an opportunity to set up an experimental situation which can be challenged by numerous influences which have been suspected of being activating or so-called "trigger mechanisms" for clinical exacerbations and recurrences. All clinicians have verified many times the precipitating influences of hyperpyrexia, either due to infection or induced by artificial means. It has been suspected that fever causes tissue alteration which temporarily interferes with or blocks antibody formation, thus causing recurrences. It could also be theorized that fever causes direct cytotoxic effects which are followed by release of virus, which spreads to other cells, thus producing recurrence by propagation.

With a reproducible carrier state, it should now be possible to test various hypotheses based on numerous clinical observations. From the standpoint of therapy for recurrent herpes simplex infection, it would appear that the most logical approach is via the development of a specific neutralizing antibody that would be stable enough to resist activating influences, such as hyperpyrexia, actinic rays, menstruation, and "nervous exhaustion."

The futility of chemotherapy for herpes simplex and other virus infections is well known. Viruses lack their own enzyme systems, using those of the host instead. Their metabolism is bound to that of the cells. They do not reproduce from their own bodies but induce the host cells to synthesize new virus material, together with normal metabolic products. Any chemotherapeutic agent capable of destroying virus must also destroy the cell which harbors it or its particles. It is conceivable that chemotherapeutic agents could be developed for the topical therapy of warts, as destruction of the proliferating host cells is desirable. Such therapy would not be applicable to chronic recurrent herpes simplex infection, and it is doubtful whether an initial attack could be aborted by a local destructive procedure.

Dr. Frank E. Cormia, New York: I thought my synapses had been stretched to the limit by some of yesterday's fine presentations, but Dr. Wheeler has further compounded the injury with this beautiful piece of work. Of course, it raises many questions to which, I hope, he will find some of the answers with additional studies.

In the first place, in some of these herpetic infections, herpes simplex and herpes zoster, the virologists tell us that there is a definite period of growth of the organism in the clinical infection. This goes on for a stated relatively short period, and then the growth ceases and the clinical infection supervenes. This is a rather amazing thing, and one wonders whether this cessation of growth is actually due to the continued mild effect of the antibodies or to some other effect, possibly something inherent in the virus itself.

As far as predisposing factors are concerned, it is a little difficult to explain why these herpetic infections develop. As Dr. Sullivan brought out, for example, in the menstrual period, about the main thing that happens in the skin, premenstrually, is increased hydration. It is hard to understand just how this would trigger off an infection.

The situation with regard to emotional and nervous stresses is even more obscure. When we come to the effect of infections, I think, we are on safer ground, because it has been observed, I am sure, by many of you, that in certain of these herpetic infections and, particularly in zoster, the administration of corticotropin (ACTH) may disseminate the infection. This is particularly true if the corticotropin is administered during the period of rapid multiplication of the virus. I imagine that this is the situation which obtains in fever and in some systemic infections.

This brings me to the last question. Why does the infection subside with continued viability of the virus? There must be some other explanation rather than that of circulating antibodies. I am sure we shall all look forward to further reports from Dr. Wheeler. Perhaps he can solve this interesting and difficult problem for us.

Dr. Carl T. Nelson, New York: I should also like to congratulate Dr. Wheeler for an extraordinarily good piece of work.

I should like to ask him if the addition of heterologous antibody, such as vaccinial antibody, will prevent subsequent herpes infection of HeLa-cells in culture. Also, will previous infection of HeLa-cell cultures with heterologous virus, such as vaccinia, prevent subsequent infection of these cells with simplex virus?

Dr. Clayton E. Wheeler, Charlottesville, Va.: There are many features of recurrent herpes simplex which are not understood, and we are using the infected tissue culture as a model to see whether we can understand some of them. Other factors than neutralizing antibody certainly operate in controlling the herpetic infection. If the only factors present were cells, virus, and neutralizing

antibody, it seems to me that the infection would continue to spread, new areas would be involved, and old ones reinvolved, until the patient would become one mass of herpes.

There are other factors which we have been considering. There is a substance (or substances) in fresh human and animal serum which destroys a small amount of herpes virus. This substance is probably not a specific antibody, since it is present in the sera of animals which have not been infected with the herpes simplex virus and it is heat labile. It seems likely that it plays some role in restricting the spread of the virus. It is intriguing to speculate whether this substance is able to enter cells. Apparently, neutralizing antibody cannot get inside cells in sufficient quantity to eliminate the virus, and perhaps this other viricidal substance may be able to do so.

Dr. Sullivan has mentioned that some cells may be susceptible to the herpes simplex virus while others may not be. This may be an important factor in limiting the spread of the virus.

Other immune mechanisms than the neutralizing effect of antibody in the serum upon herpes virus need to be considered. Patients who have recurrent herpes simplex infections show a tuberculin-type skin-test reaction to herpetic antigen. Could it be that some antigen-antibody reaction of this type destroys cells and liberates virus so that circulating antibody can eliminate the virus?

What is the herpes simplex virus doing in the tissue between recurrences? What form does this virus take at that time? Is it infectious virus but present in such small amount (and possibly mixed with neutralizing antibody) that it cannot be demonstrated by available means, or is it really immature, noninfectious virus in these cells, i. e., a true latent infection?

We have been interested in factors which might precipitate recurrent herpes simplex infections, and in a paper which will come out soon in the *Journal of Immunology*, we have described some rather interesting results. HeLa cultures were inoculated with herpes simplex virus, and one or two hours was allowed to elapse. During this time the virus entered the cells and began its growth cycle. At this time it is an immature, noninfectious virus. Cultures prepared in this manner can be incubated at 25 C for as long as a week with little or no evidence of infection or of virus production. If cultures which have been kept at 25 C are now incubated at 35 C, there promptly develops evidence of infection with the virus and of new virus production. In the tissue-culture model it appears that a latent infection may be produced by lowering the temperature of incubation and that active infection can be precipitated at will by raising the temperature of incubation. I am sure this is not altogether comparable to the course of events in recurrent herpes in man, but it does bring up possibilities for further study.

I would doubt if lowering or raising the level of neutralizing antibody in the serum is going to turn out to be an all-important factor in the precipitation of recurrent herpes or in the subsidence of the recurrence. I think that neutralizing antibody exerts a localizing and stabilizing influence and its presence may be necessary to preserve the host so that recurrences can occur, but I doubt if fluctuation in level of neutralizing antibody is a major reason for recurrent herpes.

I do not know why patients with atopic eczema tend to develop widespread infections with the herpes simplex virus (Kaposi's varicelliform eruption or eczema herpeticum). Some of the patients develop eczema herpeticum as a part of the primary infection with the virus. These patients have no neutralizing antibodies in their sera at the onset of the infection, and antibodies develop in a week or two. These patients are frequently very ill, and many of them die. Other patients with atopic eczema develop eczema herpeticum as a recurrent infection. They have had herpes simplex infections before, and their sera contain neutralizing antibodies. Most of these patients, in spite of widespread cutaneous infection, are not seriously ill, and most of them recover. It appears that the presence of antibody reduces the seriousness of the disease as far as morbidity and mortality are concerned, but it does not prevent widespread cutaneous infection. I suspect that something about the inflamed skin of the atopic makes this skin unusually susceptible to the virus, but this is pure speculation.

We have seen at least one patient with atopic eczema who had eczema herpeticum as a recurrent infection in whom cortisone may have had something to do with the appearance of the widespread cutaneous eruption. Steroid administration may in some way result in more widespread herpetic infection of the skin, just as it seems to result in more serious herpetic infection of the eye.

We have as yet done no work with heterologous antibody and heterologous virus, although this is on our agenda.

Fluorescent Material in Scales, Nails, and Hair

FRED LEVIT, M.D., Chicago

The ease with which hot water will extract fluorescent material from fluorescent hairs infected with Microsporum species [1] has led to efforts at chemical identification of the substance. Felsher [2] found it to behave as a fluorescent indicator substance. Robinson, Figge, and Bereston [3] found it to be readily water-soluble and not soluble in most fat solvents. Their spectrographic analysis led them to believe the fluorescent material to be a small peptide-like molecule. Wolf,[4] on the basis of spectrophotometric examinations, believes it to be a pteridine, although this has been questioned.[5]

Chattaway and Barlow [6] were able to extract a fluorescent material from the hair of uninfected children, which gave a chromatogram different from that obtained from infected hair. Rebell, Mahvi, and Lamb [7] were able to extract fluorescent materials from albino rat hair, which is normally fluorescent, but not from nonfluorescent hair of the 30-day-old albino rat. They also reported that paper chromatograms of boiled guinea pig, cat, and rabbit hair showed a weakly fluorescent spot.

Fluorescence under the Wood's light of tinea versicolor was investigated by Lewis and Hopper.[8] They unsuccessfully attempted to extract the fluorescent material by shaking the scales with alcohol, ether, acetone, and isotonic saline solution. This was apparently done at room temperature.

The fluorescence of nails and scales is well known,[9] although no attempt seems to have been made to extract these materials.

Experimental

Tinea Versicolor Scales.—Method: Scales were scraped from lesions of tinea versicolor, with use of the Wood's light to select areas of maximum fluorescence. Only small amounts could be obtained. They varied in color under the Wood's light from yellowish-green to yellow.

A few scales were placed in a 0.5 cm. diameter test tube and washed with several changes of ether. About 0.1 cc. of distilled water was added and the tube then placed in a boiling water bath for about 30 minutes. When volatile solvents were used, the tubes were fused shut before they were placed in the water bath.

Results: A definite though faint bluish-green fluorescence appeared in water or 0.1 N hydrochloric acid. This did not appear when xylene, acetone, or 1.0 N sodium hydroxide was used as the solvent. There was some questionable fluorescence in the solvent when brightly fluorescent scales were extracted with ether or absolute alcohol.

The fluorescent material was not removed from the water by shaking with ether. The fluorescence of the scale was very rapidly destroyed by both 20% potassium hydroxide and concentrated hydrochloric acid. The quantity of scale was too small to permit evaporation of the extracts to dryness.

Other Materials.—Method: The remaining materials used were all extracted in the same way. They were washed in several changes of tap water at room temperature, followed by several washes with acetone and ether. The ether was allowed to evaporate, after pouring off the last wash, and then distilled water was added. The flasks were then placed in a boiling water bath for periods of from 30 minutes to several hours. The final solution was filtered and the filtrate evaporated to dryness.

Results: 1. Psoriasis scales. The filtrate, which was slightly yellowish by natural light, showed a marked bluish-green fluorescence which increased in intensity as it became more concentrated. This fluorescence was not extracted from the water by shaking with ether.

When it was evaporated to dryness a brownish-yellow powder remained which fluoresced a brilliant yellowish-green. This material was not soluble in ether, acetone, carbon tetrachloride, chloroform, xylene, or carbon disulfide. It was readily soluble in water yielding a fluorescent solution. No significant change was noted in the color of the fluorescence when the pH of the solution was adjusted through a range of pH 2.7 to 8.0.

2. Exfoliative dermatitis scales (not psoriatic). The scales used were in large sheets, obtained from

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Department of Dermatology, Northwestern University Medical School (Herbert Rattner, M.D., Chairman); Toni-Gillette Fellow in Dermatology.

a single patient with exfoliative dermatitis of unknown etiology.

The filtrate had a slightly yellow tinge by natural light and had a distinct bluish-green fluorescence under the Wood's light. On evaporating to dryness a yellow crystalline powder remained which was brightly fluorescent, appearing bluish-green. It readily dissolved in water, yielding a fluorescent solution, from which the fluorescence was not extracted by shaking with ether.

The powder did not dissolve in ether, acetone, carbon tetrachloride, chloroform, xylene, or carbon disulfide.

3. Normal human hair. Normal nonfluorescent human hair was obtained from several sources, including pre- and postpubertal youngsters and adults. One batch consisted of normal dark brown adult hair which had not been shampooed or washed for three weeks. No fluorescent hairs were found before extraction, and all extraneous fluorescent materials (e. g., cotton lint) were picked out under the Wood's light before extraction. Results were the same with all the batches of hair.

A clear colorless filtrate was obtained which fluoresced a greenish-blue. On concentration the solution took on a brown tinge by natural light. When evaporated to dryness a brownish-yellow somewhat crystalline material was obtained which fluoresced a yellowish-orange. This material readily redissolved in water, yielding a fluorescent solution from which the fluorescence was not extracted by shaking with ether. The material was not soluble in ether, acetone, carbon tetrachloride, chloroform, xylene, or carbon disulfide.

When the hair extract was concentrated till the solution had a brown tinge by room light its pH was 4.0. Adjustment of the pH from 4.0 through 11.7 did not alter the fluorescence of the solution.

4. Human fingernail. Fingernail scrapings required prolonged boiling in water to obtain even slight fluorescence in the filtrate. The color was bluish-white. Evaporation to dryness left a white powdery material which was readily soluble in water but not in ether, acetone, carbon tetrachloride, or xylene.

5. Animal hairs. Black guinea pig hair (nonfluorescent) yielded a fluorescent filtrate which dried to a brown powder. This fluoresced yellow and was not soluble in ether, acetone, carbon tetrachloride, or xylene but was readily soluble in water.

Black dog hair (nonfluorescent) gave the same results as guinea pig hair except that the powder fluoresced a yellowish-orange.

Hairs from rhesus monkeys are grey at the proximal portions and shade into brown in their distal half or third. The gray portion has a faint bluish-white fluorescence, while the brown portion has a slight orange fluorescence. The filtrate obtained had a bluish-green fluorescence and dried to a light brown powder which fluoresced greenish-white. It was water soluble but not soluble in ether, carbon tetrachloride, or xylene. There seemed to be a slight amount of fluorescence in the supernate when the powder was mixed with acetone.

White rabbit hair fluoresces a brilliant bluish-white. The filtrate had a similar color under the Wood's light and dried to a slightly yellow powder which fluoresced a similar bluish-white and was readily soluble in water but not ether, acetone, carbon tetrachloride, or xylene.

6. Chicken quills. Feathers from a brown chicken were stripped from their quills, leaving a white quill with a few areas of very light brown. The white portions of the quills fluoresced a brilliant bluish-white, while the brown parts fluoresced a faint orange. Extraction with hot water yielded a filtrate which fluoresced light blue. This dried to a light brown powder which fluoresced greenish-blue and was readily soluble in water but not in ether, acetone, carbon tetrachloride, or xylene.

Comment

There appears to be a fluorescent substance or a group of fluorescent substances normally present in keratinous materials even when those materials do not themselves fluoresce. These substances are related to each other in so far as they are water-soluble but not soluble in fat solvents. They are similarly related to the fluorescent substance extracted from Microsporum-infected hairs. The precise chemical make-up of these substances remains to be determined.

In the case of scales from tinea versicolor it is not possible to state whether the fluorescence is due only to substances normally present in scale or to a substance produced through the effect of the infecting organism or to both.

Summary

Water-soluble fluorescent substances may be extracted from fluorescent scales of tinea versicolor, psoriasis, and exfoliative dermatitis, as well as from fingernails, hairs of animals and humans (whether or not they are normally fluorescent), and chicken quills. These substances are in general not soluble in the common fat solvents.

1 N. Pulaski Rd.

REFERENCES

1. Davidson, A. M., and Gregory, P. H.: Note on an Investigation into the Fluorescence of Hairs Infected by Certain Fungi, Canad. J. Res. 7:378, 1932.

2. Felsher, Z.: Observations on the Fluorescent Material in Hairs Infected by Microsporon in Tinea Capitis, J. Invest. Dermat. 12:139, 1949.

3. Robinson, H. M., Jr.; Figge, F. H. J., and Bereston, E. S.: Fluorescence of Microsporon Audouini-Infected Hair, A. M. A. Arch. Dermat. & Syph. 68:129, 1953.

4. Wolf, F. T.: Chemical Nature of the Fluorescent Pigment Produced in Microsporum-Infected Hair, Nature, London, 180:860, 1957.

5. Chattaway, F. W., and Barlow, A. J. E.: Fluorescent Substances Produced by Dermatophytes, Nature, London 181:281, 1958.

6. Chattaway, F. W., and Barlow, A. J. E.: The Fluorescent Materials Produced in Vivo by Certain Dermatophytes, J. Gen. Microbiol. 11:506, 1954.

7. Rebell, G.; Mahvi, A., and Lamb, J. H.: Paper Chromatographic Separation of Fluorescent Materials in Normal Rat Hair, J. Invest. Dermat. 27:259, 1956.

8. Lewis, G. M., and Hopper, M. E.: Pseudo-Achromia of Tinea Versicolor: Clinical and Experimental Studies and Observations on the Use of Filtered Ultraviolet Rays, Arch. Dermat. & Syph. 34:850, 1936.

9. Goodman, H.: Fluorescence: Particularly in Dermatology, Brit. J. Dermat. 40:105, 1928.

Clinical Notes, New Instruments and Techniques

Piedra

Report of a Fifth Case Originating in the U. S. A.

J. M. HITCH, M.D., Raleigh, N. C.

A survey of the literature brings to light only four previous cases diagnosed as piedra originating in the U. S. A. This would seem to justify reporting the following case.

Report of a Case

The child of an "average" urban (Raleigh) family, a white girl of 4 years without siblings, was first seen in July, 1957. Her mother reported that one week previously she had noted "dark objects" attached to several hairs of the "bangs." There were no symptoms and no treatment had been employed. Children in the neighborhood had not had a similar affliction, nor had the patient been on a trip.

According to the referring pediatrician, the child had always been in good health except for profound anemia at birth, apparently permanently corrected by one blood transfusion. Normal development had followed and the usual laboratory examinations were normal.

Cutaneous Findings.—Cutaneous examination was normal except for the scalp hair, which at its margins, particularly in the "bangs" (Fig. 1), showed isolated dark brown-black accretions on the shafts, usually on the distal one-third. There were perhaps 75 such accretions. Most hairs showed only one agglomeration. A few exhibited two. These accretions were usually about 1 mm. in length, irregularly fusiform, very hard, and completely surrounded the hair. On stroking the involved hairs, a "granular" sensation was encountered. The nodules were not fluorescent under Wood's light. The scalp and hair generally appeared normal.

Course.—The course of the disease was complete recovery in a few weeks, because the mother cut off affected hairs as they were discovered.

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Fig. 1.—Typical fusiform dark accretions on several hairs of the "bangs."

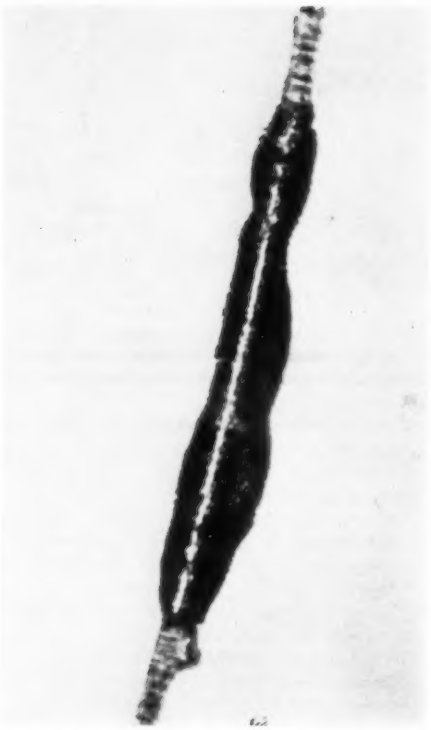


Fig. 2.—Photomicrograph of a typical piedra nodule. Enlarged × 3.5 from a mag. × 100.

Microscopic Examination.—Microscopic examination of affected hairs showed a dark brown-black lobulated fusiform accretion with a relatively smooth surface encircling an otherwise normal hair shaft. The intimate structure of these bodies was not clear other than that striations distributed radially about the hair could be detected. It could not be definitely established that these were hyphae. No spores were seen (Fig. 2).

Several attempts to produce a growth on Sabouraud's medium and blood agar (aerobic and anaerobic) were unsuccessful. Anaerobic culture on brain-heart infusion agar was negative, but on the medium treated aerobically a hair which had been washed in 70% alcohol yielded a growth beginning at the site of the nodule and spreading along the hair shaft. This colony was opaque, moist, and faintly cream-colored. It could be subcultured on the same medium. Stained slides revealed a pure culture of thin elongated bacillary forms, usually growing singly but occasionally found in short chains. The organism was usually Gram-positive but presented irregular light-staining areas having no constant distribution. With methylene blue, irregularity of staining was also a feature. The organism was not identified (Dr. T. B. Wilson).

Comment

In 1957, Daly[1] reported a case of "white piedra" originating in Vermont. He cited only three previous indigenous cases of piedra, one that of a 16-year-old youth from New York (Scott[2]) and two (in a mother and a 12-year-old daughter) also from New York, recorded by Burdick.[3] Those of Burdick were clinically "black piedra," while that of Scott was "white piedra." Since these reports, none has come to my attention.

The literature on this subject generally attributes "black piedra" to infection with Piedraia hortai and its distribution confined to tropical and subtropical regions, largely South America.

In "white piedra" it is usually stated that the distribution is not so stringently confined and that the responsible organism is Trichosporon bigelii.

In the few cases originating in this country, there has been a certain obscurity regarding the etiologic agent. In the two cases of "black piedra" reported by Burdick, cultures "consistent with piedra" were obtained on Sabouraud's medium, though it is not definitely stated that these were identified as P. hortai.

The only other indigenous case of "black piedra" which has come to my attention is that reported here. Multiple cultural studies in this case were negative except for the unidentified bacillus, which probably was not etiologically important and surely bore no resemblance to P. hortai.

In the two cases of "white piedra" reported by Scott and by Daly, repeated attempts to culture an organism were unrewarding.

Notwithstanding the inconsequential nature of the disease, its precise etiology in this country should be more clearly defined, and it is hoped that physicians who encounter the condition will make more extensive cultural studies and perhaps seek help from our experienced South American colleagues.

415 Professional Building.

REFERENCES

1. Daly, J. F.: Piedra in Vermont, A. M. A. Arch. Dermat. 75:584 (April) 1957.

2. Scott, M. J.: Piedra, A. M. A. Arch. Dermat. & Syph. 64:767 (Dec.) 1951.

3. Burdick, K. H.: Piedra in Mother and Daughter, A. M. A. Arch. Dermat. 73:386 (April) 1956.

Vibrapuncture Treatment for Creeping Eruption

JOHN van de ERVE, M.D., Charleston, S. C.

For many years various methods of destructive nature have been used in an effort to kill the larvae in the skin in the treatment of creeping eruption. These measures range from injections of phenol (necrotizing) to the commoner use of either ethyl chloride or solid carbon dioxide (Dry Ice) to cause blistering of the skin at the spot where the larvae is supposed to be. I have always preferred the use of solid carbon dioxide pencils.

All of the internal remedies suggested (including my own mistaken ideas on diethylcarbamazine citrate [Hetrazan])[1] have failed rather consistently in my practice. Therefore, a relatively painless and nonscarring method of treatment is a most welcome addition to the, at present, ineffectual methods of therapy.

Such an advance would seem to be the vibrapuncture method.[2] The ends of the trails are located and the estimated site of the larva outlined. Marking method should be a circle large enough to be beyond the needled area, or actual tattooing with the indicator may result. The trails selected for treatment should be in clear skin outside of infected purulent areas. The skin should be washed well with antiseptic solution. The area should then be covered with hydrocortisone acetate solution and, with the multiple vibrating needles set for 2-3 mm. depth, the area is thoroughly crisscrossed several times. The area to be needled may be lightly frozen with Freon or Fluoroethyl just before vibrapuncture to minimize discomfort. If this is done, hydrocortisone solution is not used.

This method has several advantages. First, while some of the skin cells are undoubtedly destroyed, the multicellular parasite larva is killed, and there is no scarring of the skin itself. Second, the antiflammatory action of the hydrocortisone tends to reduce itching and discomfort. Treatments can be repeated on those larvae escaping the first time, although the effective cure rate is much higher than with freezing, etc.

180 Wentworth St.

Submitted for publication July 25, 1958.

REFERENCES

1. van de Erve, J., Jr.: Creeping Eruption, Systemic Therapy, J. Invest. Dermat. 12:69-79 (Jan.) 1949.

2. Aaron, J. N.; Kantor, I., and Stromeyer, H.: Vibra-Puncture Technique in the Treatment of Localized Neurodermatitis, A. M. A. Arch. Dermat. 77:576-580 (May) 1958.

Control of Small Vessel Bleeding After Dermabrasive Surgery

MURRY M. ROBINSON, M.D., Washington, D. C.

Numerous refinements of techniques have been developed in abrasive surgery since it was first introduced, in 1952, by Kurtin. Most of these refinements, however, have benefited the operator rather than the patient. Ethyl chloride as the refrigerant has given way to Freon 114 (dichlorotetrafluoroethane) or to combinations of Freon 114 and ethyl chloride. New abrasives have been developed or adapted to this procedure, but in experienced hands all of these abrasives can be used interchangeably. Further improvement in techniques will be developed.

The most pressing advances should be directed toward patient comfort. The operation is not truly painful, but there are uncomfortable features, such as apprehension which sometimes borders on fear. Much of the apprehension has been allayed by the elimination of the blower when ethyl chloride was replaced by Freon and by the use of preoperative sedation and analgesics. The most uncomfortable feature, however, is the crust which develops after the operation. This crust, which is thick and stiff, makes eating, laughing, and other facial movements difficult and uncomfortable. Any method that could possibly make this crust thinner and more pliable would greatly ease the postoperative discomfort. Since the thickness of the crust depends on the amount of small vessel bleeding, a decrease in this bleeding should ease the discomfort follow-

Submitted for publication July 29, 1958.

ing the operation. With this in mind, an attempt was made to find a drug or combination of drugs that would decrease this small vessel bleeding.

The following is a report on a controlled study of 10 patients involving 20 abrasive operations treated pre- and postoperatively with a combination of adrenochrome semicarbazone, present as 65.0 mg. of carbazochrome salicylate, 5.0 mg. of menadiol sodium diphosphate (vitamin K analogue), 50.0 mg. of purified hesperidin, and 100 mg. of ascorbic acid.

Pharmacology of Constituents

1. *Carbazochrome Salicylate.*—Adrenochrome is an oxidation product of epinephrine. It was isolated in 1937[1] and has the same hemostatic action of epinephrine but does not alter blood pressure, cardiac rate, or volume.[2-4]

Adrenochrome itself is unstable in solution, but a derivative, the monosemicarbazone of adrenochrome, when combined with a sodium salicylate complex, produced a compound which is both stable and soluble and is equally as hemostatic as adrenochrome semicarbazone. Its mode of action seems to be by increasing the resistance of the capillaries and promoting the retraction of severed capillary ends.[5] One would, therefore, expect it to be used wherever bleeding occurs from a broad vascular base, and it would seem that it is particularly suitable for the control of bleeding after dermabrasive surgery.[6]

2. *Hesperidin.*—This product has been of value alone and in combination with ascorbic acid (vitamin C) in most diseases associated with capillary fragility and hemorrhagic diathesis. Its supposed method of action is to increase capillary resistance and overcome capillary permeability and fragility by maintaining the integrity of the cement of the capillary walls.

3. *Menadiol Sodium Diphosphate.*—Menadiol sodium diphosphate is stable and rapidly absorbed and has a greater antihemorrhagic activity than fat-soluble menadione.[7] It restores the prothrombin level to normal when it is depressed by any means and has, therefore, become routine by many before and after surgery.[8]

It is expected that the combination of these drugs should decrease the bleeding following abrasive surgery. The results of the following experiment justify this expectation.

Procedure

Ten patients with postacne scarring were operated on initially by the Kurtin method without the use of the above drug combination. These same patients were then abraded after an interval of six to eight weeks under the influence of this hemostatic combination of drugs. One capsule was administered three times daily before the operation and for three days postoperatively. Photographs were taken of each patient 10-15 minutes following the operation and 2 days postoperatively. This 10-15 minute interval was necessary in order that the hemostasis due to the freezing would not be a complicating factor in judging the results. If photographs are taken up to six minutes after abrasion, the hemostasis due to the freezing would make it seem that the drug used gives better results than is actually the case. In this way all of these patients acted as their own controls.

Results

Without exception, all of these patients reacted in the same way without the use of the drugs. Bleeding was copious, and the resultant crust was thick and stiff. Cracks developed in the crust and frequently left lines in the skin underneath these cracks. The time required for the crust to separate completely was 10-14 days. When the hemostatic drug combination was administered pre- and postoperatively, the small vessel bleeding was decreased by about 50% and the resultant crust was considerably thinner and more pliable. The time necessary for the crust to separate completely was reduced to 8-11 days. The patient was more comfortable and could eat with greater facility. In addition, the deep cracks which frequently occur in the thicker crust and which result in lines in the new skin developing beneath it did not occur as easily and as frequently in this thinner crust, therefore, decreasing the incidence of these resulting lines.

Summary and Conclusion

The use of adrenochrome semicarbazone, carbazochrome salicylate, menadiol sodium diphosphate, purified hesperidin, and ascorbic acid pre- and postoperatively resulted in decreased bleeding and as a result of this decreased bleeding in a thinner and more pliable crust. The combination of these two results decreased the postoperative discomfort to the patient. No cases of sensitivity to the drug or any side-effects have been observed.

The drugs tested were supplied under the name of Adrestat by Mr. Kenneth Ericson, of Organon Laboratories.

Farragut Medical Building (6).

REFERENCES

1. Green, D. E., and Richter, D.: Biochem. J. 31:596, 1937.

2. Bacq, Z. M.: Compt. rend. Soc. biol. 141: 536, 1947.

3. Bacq, Z. M.: Presse méd. 55:175, 1947.

4. Pulaski, E. J., Reichel, H., and Voorhees, A. B., Jr.: Proc. Soc. Exper. Biol. & Med. 70:504, 1949.

5. Bacala, J. C.: West. J. Surg. 64:88, 1956.

6. Brown, W. S.: Northwest Med. 57:470-473 (April) 1958.

7. Allen, J. G.: Am. J. M. Sc. 205:97, 1943.

8. Dam, H., and Plum, P.: Postgrad. Med. 15:279, 1954.

Prednisolone in Aerosol Form

FREDERICK REISS, M.D., and ANDREW KALLOS, M.D., New York

A prednisolone (Meti-Derm) aerosol, containing 50 mg. of prednisolone, isopropyl myristate, and Freon as a propellant* was used in 109 patients with selected dermatoses.

The following patients were treated: 62 with contact dermatitis, 17 with atopic dermatitis, 16 with seborrhoic dermatitis, 6 with pruritus ani, 2 with circumscribed neurodermatitis, 2 with dyshidrotic eczema, 1 with eczema scroti, 1 with pruritic psoriasis, 1 with essential pruritus, and 1 with otitis externa eczematosa.

Patients applied the spray at least twice daily and oftener, as needed, when itching was severe. Spraying the affected area for three seconds delivers approximately 0.5 mg. of prednisolone.

Submitted for publication May 10, 1958.

*A supply was made available for this study by G. Kenneth Hawkins, M.D., Division of Clinical Research, Schering Corporation, Bloomfield, N. J.

Results were good (both subjective and objective improvement) in 63 patients and fair (relief from itching only) in 26 patients, or 82% over-all improvement. Nineteen patients showed no response. In one case of essential pruritus, itching increased, but sensitivity did not occur in a single instance. Of 61 patients who were treated with both Meti-Derm cream and aerosol, 95% considered Meti-Derm aerosol to be equal or in some cases even superior. Placebo spray was employed in five patients with no effect. Meti-Derm aerosol is especially suitable for large and hairy areas and is particularly convenient for patients who must handle paper or other stainable material during the working day. The distinct cooling produced by Freon also enhances the antipruritic effect of prednisolone.

870 Fifth Ave. (21).

Prednisolone (Meti-Derm) as an Aerosol for Dermatoses

HARRY M. ROBINSON SR., M.D., Baltimore

Topical applications of hydrocortisone[1] and, more recently, prednisone or prednisolone[2-4] are widely used in the treatment of many types of dermatologic disease. A new vehicle for prednisolone (Meti-Derm) aerosol with 50 mg. of the steroid, isopropyl myristate, and Freon as a propellant, in a 150 gm. spray applicator, was made available to us for clinical study. A three-second spray delivers approximately 0.5 mg. of prednisolone.

Submitted for publication July 9, 1958.

Clinical research supplies for this study were received from G. Kenneth Hawkins, M.D., of the Division of Clinical Research, Schering Corporation, Bloomfield, N. J.

Method

This series consisted of 79 patients with dermatologic disease, most commonly eczema of various types, including eczematous dermatitis. Patients were instructed to apply the aerosol to lesions in very short bursts of spray from a distance of 1 to 2 in. Examinations were made weekly and progress noted. No other therapy was used.

Results were graded as "excellent" if lesions involuted promptly and completely, "good" if re-

sponse was somewhat slower or not complete, "fair" if some objective response occurred, and "poor" if the condition was not affected. There was also a separate category for patients who reported relief of itching but in whom the lesions were unimproved. In no case did prednisolone aerosol worsen the disease or cause side-effects.

Results

The results are summarized in the Table. Good or excellent results occurred in a total of 65 patients (82.3%).

In one patient with stasis eczema, the ulcer was not affected, but the surrounding dermatitis cleared; in this case we considered the response as "fair."

In 39 of these 79 patients only one week of therapy was necessary, after which time the lesions were cleared. In the other patients two to four weeks were required; in these instances the acute phase usually cleared rapidly, but further therapy was attempted for the more resistant areas.

We had some patients for whom the aerosol was prescribed chiefly to relieve pruritus, since we could not expect that it would affect the primary condition. Nine patients reported marked relief of itching associated with the following conditions: epidermophytosis, dermatitis herpetiformis, erythema multiforme, granuloma pyogenicum, hidradenitis suppurativa, and xanthoma.

A bilateral paired comparison, on similarly involved areas in 12 patients, was made of prednisolone aerosol and a placebo spray. The placebo gave some transient relief of pruritus; however, the prednisolone aerosol was clearly superior.

The aerosol appears to have several important advantages over other topical therapies and is especially satisfactory for inflammatory lesions. Involution of these lesions occurred more rapidly than is usual with creams or ointments.

There also seems to be more marked relief of pruritus with the aerosol than with creams or ointments. The cooling effect itself may be a healing factor, enhancing both the antipruritic and anti-inflammatory activity of prednisolone, as shown by a report[5] of good results with cryotherapy in dermatitis venenata and other vesicular dermatoses. The mechanism of action may be a combination of ischemia in the affected area and rupture of the vesicular wall with subsequent discharge of the contents.[5]

Patients appreciated the fact that prednisolone aerosol is nongreasy and nonstaining, and lesions need not be touched. If used properly the aerosol lasts longer than comparable amounts of cream and is more uniformly applied. This new vehicle is especially efficient when large surfaces or hairy areas must be treated. No side-effects were observed.

106 E. Chase St. (2).

REFERENCES

1. Sulzberger, M. B., and Witten, V. H.: Hydrocortisone Ointment in Dermatological Therapy, M. Clin. North America 38:321-336 (March) 1954.

Results of Therapy with Prednisolone Aerosol

Diagnosis	Patients, No.	Excellent	Good	Pruritus Relieved	Fair	Poor
Rosacea	2	--	2	--	--	--
Dermatitis, contact	8	4	4	--	--	--
Dermatitis, eczematous	34	24	10	--	--	--
Dermatitis herpetiformis	1	--	--	1	--	--
Epidermophytosis	2	--	--	2	--	--
Erythema multiforme	1	--	--	1	--	--
Eczema	5	5	--	--	--	--
Eczema, atopic	4	4	--	--	--	--
Eczema erythematosum	1	1	--	--	--	--
Eczema, seborrheic	2	1	1	--	--	--
Eczema, stasis	4	2	--	--	2	--
Eczema with epidermophytosis	2	--	--	2	--	--
Eczema with folliculitis	3	--	3	--	--	--
Folliculitis with pyoderma	1	--	1	--	--	--
Granuloma pyogenicum	1	--	--	1	--	--
Hidradenitis suppurativa	1	--	--	1	--	--
Neurodermatitis	1	1	--	--	--	--
Onycholysis	1	--	--	--	--	1
Paronychia	2	2	--	--	--	--
Scleroderma	2	--	--	--	--	2
Xanthoma	1	--	--	1	--	--
Total	79	44 (55.7%)	21 (26.6%)	9 (11.4%)	2 (2.5%)	3 (3.8%)

2. Frank, L., and Stritzler, C.: Prednisolone Topically and Systemically, A. M. A. Arch. Dermat. 72:547-549 (Dec.) 1955.

3. Goldman, L.; Flatt, R., and Baskett, J.: Assay Technics for Local Anti-Inflammatory Activity in the Skin of Man with Prednisone and Prednisolone, J. Invest. Dermat. 25:75-76 (Aug.) 1955.

4. Zimmerman, E. H.: Therapeutic Assay of Topically Applied Prednisolone Alcohol in Selected Dermatoses, J. A. M. A. 162:1379-1381 (Dec. 8) 1956.

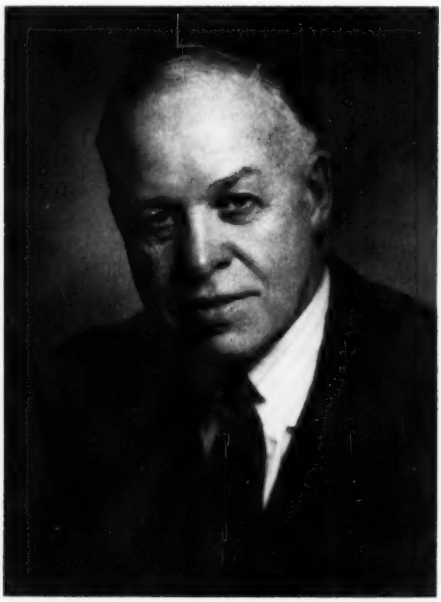
5. Robinson, M. M.: The Treatment of Dermatitis Venenata (Rhus) by Cryotherapy, J. Invest. Dermat. 8:239-243 (May) 1947.

Obituaries

EMERSON JAMES TROW, M.D.
1886-1958

Born in Stratford, Ont., Canada, Emerson Trow graduated in medicine from the University of Toronto in 1908. After a few years in general practice he commenced graduate work in his chosen specialty at the New York Skin and Cancer and Bellevue Hospitals and in the office of the late L. Duncan Bulkley, where he numbered among his friends Drs. Paul Bechet and the late Fred Wise.

He returned to Toronto to establish a practice in dermatology in 1913, but World War I interrupted this for a few years. In 1918, he was appointed to the teaching staff of the University of Toronto and taught undergraduates and graduates until his retirement, in 1949. He succeeded the late Dr. King Smith as head of the department of Dermatology in 1929.



EMERSON JAMES TROW, M.D.
1886-1958

Dr. Trow took a keen interest in the Academy of Medicine, Toronto, where he served in many capacities including that of chairman of the Section of Dermatology, 1955-1956. He was elected to the American Dermatological Association in 1931 and was vice-president in 1947-1948 and Fellow of the Royal College of Physicians and Surgeons of Canada in 1930. He was a founder member of the Canadian Branch of the British Association of Dermatology, which, in 1947, became the Canadian Dermatological Association, and always took a keen interest

in this young society. In 1955, he was made honorary member of the Dermatological Section of the Royal Society of Medicine, London, England. He was a founder member of the American Academy of Dermatology and Syphilology, in which he took a great interest, and he attended most of the meetings. He served a three-year term as director, 1951-1954.

Dr. Trow wrote extensively on dermatology and syphilis in his younger years, but his imprint in his chosen field will be his lasting influence on medical students and particularly on dermatologists who worked with him. He was a great humanitarian, keenly interested in his patients and especially in dermatology and young dermatologists. His kindliness was renowned, and he had a *joie de vivre* which was not quenched, even in his long fatal illness.

He attended the International Congress of Dermatology in Stockholm in 1957 and was interested and enthusiastic about the Congress and especially the clinical presentations. He was a keen photographer and brought back with him many color pictures of his journey through Europe.

His family life was a happy one. He leaves a widow, a son, Dr. E. James Trow Jr., also a dermatologist, three daughters, and ten grandchildren, all residing in Toronto.

Canadian Dermatology has lost a true friend and staunch supporter, and American Dermatology is richer and better for having known Emerson Trow.

NORMAN M. WRONG, M.D.

Society Transactions

BRONX DERMATOLOGICAL SOCIETY

Morris Leider, M.D., President
Henry Silver, M.D., Secretary
March 20, 1958

Ichthyosis (Result of Treatment with a 10% Sodium Chloride Ointment). Presented by Dr. Irwim I. Lubowe and Dr. Edward H. Mandel.

A 5-year-old boy has had a generalized skin eruption since birth. A maternal uncle had a similar condition. No other members of the family are affected.

The eruption consists of dry scaling in the characteristic fashion of ichthyosis.

The patient applied 10% sodium chloride in hydrophilic ointment to the right upper and lower extremities daily for about three months. The other limbs were left untreated. There is marked improvement on the treated side.

Discussion

Dr. Hyman Gordon (by invitation): In the *Acta medica scandinavica* (108:98, 1941) Ljungstrom reported "A Simple and Effective Treatment of Ichthyosis." Observing that a 22-year-old man with ichthyosis hystrix was free of lesions in the axillae, where he sweated profusely, Ljungstrom reasoned that sodium chloride could be the preventive or improving agent of ichthyosis. He recommended to his patient baths of 3% salt water followed by inunction of 10% sodium chloride in lanolin. Within a month his patient was free of lesions.

I have employed the same treatment to one case of ichthyosis vulgaris and another of ichthyosis hystrix. Both responded dramatically; in the latter, a "porcupine man" was rehumanized. These cases have been reported in the *Archives of Dermatology and Syphilology* (52:178, 1945).

Dr. Arthur Hyman and Dr. Alexander Fisher tell me that they have had equally good results.

I am reminded that this effective treatment confirms points made by Dr. Helen Curth and Dr. David Bloom in their presentations on genodermatoses at the March meeting of this Society to the effect that diseases of genetic pathomechanism are not hopeless and sometimes are very easily helped.

Dr. Abraham J. Orfuss: May I report the follow-up of a case of ichthyosis I recently presented before this Society after treatment with sodium chloride ointment. I used the sodium chloride ointment on one arm and the vehicle of the ointment on the other. Both sides seemed to respond well, and I have since ordered the vehicle to be applied alone. The improvement is maintained. I am aware that this contradicts recent experience which seems to prove that sodium chloride ointments are superior to simple greases. I think it can be said that mild cases of ichthyosis do well enough with simple greases but that severe grades do better with sodium chloride ointments.

Tuberculid of the Skin. Presented by Dr. Abraham J. Orfuss.

A white woman, aged 41 years, has been under observation since 1949. She complains of symptomless, discrete, red papules occurring on various parts of the face in crops for the past 10 years. Her health in general has been good. There is no history of tuberculosis or other constitutional disease.

The patient presents scattered, discrete and clustered, erythematous papules on the forehead, paranasal areas, and chin. No apple jelly papules are found on diascopy.

A biopsy specimen obtained in 1949 was interpreted by Dr. W. Sachs as follows: "This may be a lupus miliaris disseminatus faciei but I cannot rule out the tuberculid of Lewandowsky. Throughout the cutis are found numerous collections of epithelioid cells in tubercle formations, edema, and an infiltrate of small, round, and wandering connective tissue cells. No necrosis is seen. The epidermis reveals no change."

The patient has had gold and bismuth injections, arsenic, calciferol, chloroquine, topical lotions, topical corticosteroids, and isoniazid, always with recurrence in the form of crops of erythematous papules. Suggestions for further therapy are requested.

Discussion

Dr. Hans H. Biberstein: Dr. Hyman asks me how many kinds of tuberculids of the face I know. I cannot give a definite figure. The tuberculids of the face have a variety of features: macular

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lupus vulgaris-like lesions level with the skin surface and distributed over the mandibular regions and adjacent areas of the neck, or micropapular lesions symmetrically arranged in the preauricular and temple regions, or larger papules sometimes densely arranged in a rosacea-like setting, or papulo-necrotic or nodular lesions set slightly deeper in the skin. In addition, features may develop which could be considered as connecting links between actual tuberculids and tuberculosis, such as acne telangiectodes (Kaposi) and lupus miliaris (or follicularis) of the face; these are accepted as tuberculoses by some and classified as tuberculids by others. A diagram in Lewandowsky's "Die Tuberkulose der Haut" (page 79) illustrates the theoretical relationship.

With regard to the case in point, I would regard it clinically as a possible atypical (asymmetrical) case of Pringle's disease, but the histology, which is that of a tuberculoderm, must be accepted as decisive.

Lupus Erythematosus. Presented by Dr. Frances Pascher and Dr. Sidney G. Clyman (by invitation).

A 16-year-old white girl was first seen nearly two years ago with a history of a persistent red flush of 10 days' duration over the nose and upper part of the cheeks. She had no other complaint and felt in excellent health.

An ill-defined erythema in a butterfly distribution was found over the nose and malar portion of the cheeks. No follicular plugging or scaling were seen. The erythema subsided promptly and cleared within three weeks of treatment with Aralen phosphate (250 mg. b. i. d.) and with the use of sun-screen lotion. All treatment was discontinued in four months. The eruption recurred three months ago, after exposure to cold and wind. Spontaneous fluctuations in the degree of erythema have been observed. There have been no other symptoms.

An L. E. test (Magath technique) was positive two years ago and negative subsequently on three consecutive occasions (two, three, and six months later). A marked positive L. E. test was obtained three months ago with the Zinkham-Conley technique. In the beginning, two years ago, a doubtful flocculation reaction and anticomplementary serological tests "typical of patients with L. E." (Dr. Kostant) were obtained. Determination of the sedimentation rates showed successive elevations: 32 mm., 25 mm., and 60 mm. in an hour. Repeated urinalyses and hemograms showed no abnormalities. Total protein, A/G ratio, and cryoglobulin studies gave normal results.

Discussion

Dr. Frances Pascher: A striking feature of this case is the disparity between the clinical signs and the laboratory findings. The patient has no symptoms other than the eruption on the face, and yet we find a consistent elevation in the sedimentation rate, "biologic false" positive serologic test for syphilis, and two positive L. E. tests out of five performed. In view of these findings this case must be classified as systemic lupus erythematosus.

All other conditions known sometimes to be attended by a "false positive" L. E. test can be excluded. This patient did not get penicillin or hydralazine, nor does she show any evidence of generalized scleroderma. I mention the latter particularly in view of a recent experience with a case on Dr. Arthur Hyman's service of generalized scleroderma with a positive L. E. phenomenon. The finding of unequivocal positive L. E. tests in the case presented is interesting also in light of the repeated negative tests obtained in some cases of acute and subacute systemic lupus erythematosus in which the clinical manifestations are much more striking.

The laboratory findings are not only of diagnostic importance but bear directly on management. This patient should be protected from avoidable stress, e. g., undue exposure to sunlight, extreme cold, elective operations. She should not have penicillin. I might also add that injections of typhoid vaccine should be avoided. At a recently held symposium at the New York Skin and Cancer Unit on Lupus Erythematosus, Dr. Lewis Thomas told of deaths within minutes after the administration of this vaccine in patients with systemic lupus erythematosus.

Dr. Abraham J. Orfuss: I would like to ask a serologist to explain that serologic reaction the nature of which "fits in with the pattern seen in lupus erythematosus." I did not know that there was a pattern of such specificity.

Dr. George H. Kostant: A serologic pattern not infrequently associated with lupus erythematosus is one in which the crude lipoidal antigens in the flocculation tests (e. g., Mazzini) are *reactive*, the purified cardiolipin antigens (e. g., VDRL), are *nonreactive*, and the complement-fixation procedures are anticomplementary. In many instances we have been able to predict a clinical diagnosis of lupus erythematosus solely from this serologic pattern.

Dr. Hans H. Biberstein: The patient clinically shows the features of that variety of lupus erythematosus which was called erysipelas perstans (Kaposi) or erythema perstans faciei (Jadassohn). In contrast to erythema centrifugum, which may develop into chronic discoid lupus erythematosus, the condition described by Kaposi and Jadassohn may change into acute lupus erythematosus. This old clinical experience is supported in this case by the laboratory findings of L. E. cells, increased sedimentation rate, and false-positive seroreaction

in a patient who, except for the erythema of the face, still seems to be in good health as far as one can tell.

Urticarial Sensitivity to ACTH. Presented by Dr. Conrad Stritzler.

A 40-year-old woman is presented with a history of atopic dermatitis of the hands and forearms since childhood. Local therapy has been ineffective. For the past three years, with good results, she has been on intermittent therapy with prednisone and ACTH in a gelatin vehicle.

About 6 months ago, 20 minutes after an intramuscular injection of 40 units of ACTH gel, the patient experienced generalized itching, swelling of the lids and lips, and difficulty in breathing. This persisted for an hour, and was finally cleared by an injection of epinephrine.

No more ACTH was given until a month ago, when a test dose of 4 units of ACTH was administered. The patient again developed generalized itching and urticaria, but she had no difficulty in breathing. This, too, subsided following an injection of 0.25 cc. epinephrine 1:1000.

A passive transfer test was positive; controls with serum from a patient not sensitive to ACTH were negative. Scratch tests were positive to beef and pork ACTH but negative to gelatin and to beef and pork antigen as commercially purveyed.

Therapy with prednisone orally is well tolerated and has kept the dermatitis under control with maintenance doses of 7.5 to 10 mg. daily.

Discussion

Dr. Frederick Reiss: The negative scratch tests to ordinary pork and beef antigens do not exclude the possibility of sensitivity to ACTH per se; as a matter of fact, the positive reactions to ACTH from both pork and beef suggest that the ACTH itself is the specific antigen. ACTH is a polypeptide, and if it could be used as such to test with, i. e., without anything extraneous from its animal source, I would expect a positive reaction.

Dr. Franz Herrmann: Urticarial eruptions in response to ACTH administration have been carefully studied. In some instances the reaction was avoidable by switching from ACTH obtained from one species of animal (e. g., cows) to ACTH of another species (e. g., pigs), whereas in others the response was produced by any ACTH preparation. (See Brown, E. M., and Hollander, J. L.: Allergy to ACTH and the Use of Beef ACTH, and discussions by C. R. Stevenson and by S. Feinberg, in Proceedings of the Second Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1951, Vol. 2, Chap. 9, p. 391.)

Keloid Following Circumcision. Presented by Dr. Louis Wexler.

A 23-month-old white boy was first seen at seven months of age because of a mass on the prepuce. This lesion appeared shortly after circumcision and has been gradually getting larger.

When the child was born, there was a skin defect of the scalp in the midline. This closed fairly rapidly by granulation and scar formation. He also has congenital bilateral cataracts, which do not appear to greatly interfere with his vision.

Examination when first seen revealed a ring of scar completely encircling the penis. It was about 1 cm. in width and approximately 0.5 cm. in thickness. It had a hard consistency and the appearance of a keloid. In addition, there were several nodules on the surface, which were raised above the rest of the mass, but with the same general characteristics. This lesion continued to enlarge, and excision was deemed necessary. The operation was performed 10 months ago. At that time the annular mass was raised 1.5 cm. at its lowest points and more where the nodules were present. Following excision, the edges of the skin were approximated and sutured. An ointment containing prednisolone was applied to the dressings.

The pathologist who examined the operative specimen reported: "Definitive differentiation between fibroma and keloid is not possible."

Immediately after surgery, well-shielded irradiation was given, to a total of 375 r in three fractional treatments. The scar was imperceptible until last month, when enlargement again began.

This case is being presented for advice as to further management.

Discussion

Dr. Abraham J. Orfuss: My impression is that the dose of 375 r delivered postoperatively to prevent re-formation of the keloid was inadequate. If radiation had been decided upon, then, I think, a dosage of ¾ of a skin unit once every three weeks for a total of three treatments (about 600 to 700 r) would have been adequate.

Dr. Norman Orentreich: Resistant keloids will frequently respond to local injection of steroids combined with cryotherapy by solid carbon dioxide. It is extremely unwise to treat the penis with x-rays. Under local anesthesia the keloid could be frozen by strong application of carbon dioxide and then injected with 0.2 cc. of hydrocortisone or prednisolone acetate (25 mg. per cc.), sites 1 cm. apart. This treatment could be repeated each month until the lesion responds.

Dr. Frances Pascher: I would like to suggest thorium X for this patient. Alpha-radiation would certainly be preferable to γ-radiation in this situation.

Leukemia Cutis; Lymphocytic Infiltration? Presented by Dr. A. J. Orfuss.

A 70-year-old white woman has had persistent and slowly progressive skin lesions on the back and the left arm for the past three years. Her health in general has been good. There are no constitutional symptoms, except for vague generalized pains on occasions. There has been no anorexia, weight loss, or weakness.

Upon examination, one sees on the left midback and on the left arm discrete, well-defined nodular masses that are sharply circumscribed, erythematous and edematous, fleshy, and solid. There is no adenopathy. The liver and spleen are not palpable.

Laboratory studies reveal a normal pattern in the peripheral blood and a reasonably normal chest plate.

A biopsy section of the skin was interpreted by Dr. Charles Sims as follows: "The corium throughout presents a diffuse and patchy infiltration composed of, for the most part, fairly uniform lymphocytes among which are scattered red blood cells. In addition, there are numerous histiocytes present. Edema of the connective tissue framework is noted in some areas. The vessels in most of the section are dilated and the walls are edematous. The epidermis is thinned in part with obliteration of the rete pegs. The diagnostic possibilities are two, namely, leukemia cutis and lymphocytic infiltration."

The patient has had but one treatment of 150 r to each lesion four weeks ago.

Discussion

Dr. Max Wolf: The interpretation of these persistent plaques as manifestations of lymphocytoma cutis would be justified if the microscopic picture would reveal germinal centers of epithelioid cells surrounded by lymphocytes. The diffuse infiltration of the upper cutis with lymphocytes in this case corresponds more to the findings in lymphocytic infiltration, although lesions of lymphocytic infiltration are usually evanescent, whereas those in this case have persisted.

Dr. Frances Pascher: I'm afraid I cannot feel as sanguine about the prognosis in this case as our Chairman is. I have followed cases of this type where the number of lesions gradually increased and the ultimate cause of death within a period of a few years was either lymphosarcoma or lymphatic leukemia. I agree that a diagnosis of leukemia cutis cannot be made in the presence of a normal hemogram. The lesions and the histologic picture are that of a lymphoma. The presence of considerable numbers of histiocytes as well as mature lymphocytes and the distribution and configuration of the infiltrate suggest a malignant lymphoma rather than a benign process. Radiation confined to the lesions as carried out by the presenter is the only treatment indicated at this time. Certainly, cytotoxic drugs should be withheld until there is evidence of systematization. I agree with the speaker who said that the patient should not and need not be made aware of dire possibilities at this time. The physician, however, should be aware that prognosis must be guarded.

Xanthoma Tuberosum Multiplex with Hyperlipemia (Hypercholesteremic Xanthomatosis). Presented by Dr. Conrad Stritzler.

A housewife, age 58, is presented with grouped, orange-colored nodules about both elbows and yellow streaks on both palms of many years' duration. Her mother died at age 57 of malignancy and her father at the age of 84, presumably of senility. No other members of the family are known to have a similar condition or diabetes, coronary disease, or liver disease. No blood studies have been done on members of her family to determine whether any have lipemia without cutaneous manifestations.

The patient's general health was good until August, 1957, when she had an episode of chest pain which was diagnosed as acute coronary thrombosis. She was later found, on x-ray study, to have a diaphragmatic hernia, but this has been asymptomatic.

Laboratory studies to date have revealed a milky, yellowish serum, cholesterol of 430 mg., cholesterol esters of 120 mg., total lipids of 2840 mg., sugar of 118 mg., and total proteins of 7.2 gm., with a normal A/G ratio. Biopsy of a xanthoma revealed an infiltration of histiocytes filled with lipid, and Touton foreign body giant cells.

By way of treatment, for the past week the patient has been taking a nicotinic acid preparation (1.0 gm. t. i. d.). She is also on moderate fat restriction. Ten milligrams of heparin was given intravenously, and fifty milligrams of heparin was injected into the patch of nodules on the right elbow yesterday.

Discussion

Dr. Franz Herrmann: The creamy serum and the history do not leave any doubt that the xanthomatosis in this patient is caused by idiopathic hyperlipemia rather than by "primary familial" ("essential") hypercholesteremia. Both types are familial and both follow the "incompletely dominant" pattern of inheritance.

Case for Diagnosis: Dermatitis Medicamentosa? Presented by Dr. Frederick Reiss.

Syphilitic Aortic Regurgitation. Presented by Dr. Conrad Stritzler.

CHICAGO DERMATOLOGICAL SOCIETY

Samuel M. Bluefarb, M.D., President
Frederick J. Szymanski, M.D., Secretary
Feb. 19, 1958

Progeria (Hutchinson-Gilford Syndrome). Presented by DR. ADOLPH ROSTENBERG and (by invitation) DR. IRA ROSENTHAL.

Medical history: This child was of normal birth weight. Her parents noted poor weight gain by the age of 4 months. Her hands were noted to be abnormal at birth. A diagnosis of progeria (Hutchinson-Gilford syndrome) was made at the age of 4 months. Weight gain and growth have been poor. The child now weighs 10 lb. She is in the hospital at present for treatment of a corneal ulcer. Child is believed to be of low-normal intelligence.

Description: The child shows marked paucity of subcutaneous tissue. There is almost complete alopecia. There are flexion contractures of the hands, knees, and ankles. The ears are deformed, and the ear lobes are missing. The splanchnicranium is poorly developed. Fontanels are still open.

Laboratory data: Routine tests all normal. Slight amino-aciduria.

Treatment: None.

Discussion

DR. IRA M. ROSENTHAL (by invitation): Progeria was first described by Hutchinson in 1886. Not much had been added since that time to his description. Hutchinson noted the small body, the underdeveloped jaws, and the alopecia which are part of the disease. He also noted the contractures. As cases of progeria were followed, it became evident that premature atherosclerosis was part of the disease. Progeria derives its name from "premature aging." It is unlikely, however, that progeria is a manifestation of premature senilism. We have had the opportunity to study three of these cases, of which this patient is the third. We feel, as does Dr. Talbot, that progeria is a disease of metabolism and not a simple manifestation of premature aging. It is evident that premature atherosclerosis occurs in many conditions in which true premature aging is not found. The striking appearance resembling senilism found in progeria is caused by the alopecia, the poor nutrition, and the lack of adequate growth of the jaws. Serial cephalometric roentgenograms of the skull have demonstrated that the abnormal facial appearance results from inadequate growth of the jaws.

It is generally accepted that these children are normal up to the age of 15 or 18 months, after which the symptoms of progeria become manifest. The diagnosis in this case was made at the age of 3 months. This child at no time had any hair. This is in contrast to other cases described in which hair was present originally and was subsequently lost. The contractures found in progeria have been considered to be the result of senile osteoarthritis. We believe this idea is erroneous. It is more likely that the contractures are periarticular in origin. It is of interest that the contractures in this child were present at birth.

The basic metabolic error in progeria is entirely unknown.

DR. BLUEFARB: How long do they live?

DR. ROSENTHAL: They live from 15 to 25 years. They die of the complications of coronary heart disease, usually of myocardial infarction. Patients with progeria are usually of normal intelligence. This patient is somewhat retarded.

DR. CORNBLEET: Have you considered the possibility of amino-aciduria in these cases?

DR. ROSENTHAL: Paper chromatography did disclose that this patient does have a mild degree of amino-aciduria. There are, of course, many causes for amino-aciduria. I do not believe that there is a direct relation to her poor growth. The average case of progeria attains a weight of 25 to 30 lb. This patient is one of the smallest cases of progeria on record. From a study of her growth pattern, we doubt that she will grow very much more.

DR. ROTHMAN: In cases that have come to autopsy, did the examination include the central nervous system?

DR. ROSENTHAL: Yes. This was done in several cases. In each case the brain was normal. Atherosclerosis has been found in every case in which necropsy has been performed.

DR. ADOLPH ROSTENBERG: I thought this case would be interesting to show, even though we are not likely to see another. Gilford coined the term progeria because he thought there were signs of premature senility. Previously it had been called micromegaly because it was thought to be the antithesis of acromegaly.

One theory to which Dr. Rosenthal did not allude, probably because it is not too well established, is that the condition arises because of hypofunction of the eosinophilic cells in the pituitary.

Has progeria any relationship to patients we see? Werner's syndrome is sometimes called progeria of the adult. This is a misapplied name. Werner's

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syndrome is said to be associated with scleroderma, but these persons really do not have scleroderma. They have some atrophy of the skin which comes close to what you see in acrodermatitis chronica atrophicans. Werner's syndrome so far as is known has nothing to do with progeria of the child.

Acanthosis Nigricans, Juvenile Type, Combined with Necrobiosis Lipoidica Diabeticorum. Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. YELVA LYNFIELD.

A 28-year-old white housewife was presented to this Society in February, 1953, because of her acanthosis nigricans and signs of hypercorticoidism, such as excessive obesity, hypertrichosis, violaceous striae, flushing of face, and alimentary glycosuria.

At age 10, following a head injury, she began to gain weight, gradually stabilizing at 250-275 lb. Her acanthosis nigricans developed at about the age of 11. It was diagnosed clinically and histologically by Drs. Webster and Grimm in 1950. Since menarche at age 13, her menses have been irregular. Diagnosis of polycystic ovaries and later of Stein-Leventhal syndrome was made in Michael Reese Hospital. Her facial hypertrichosis has increased markedly in the past year.

In 1950, asymptomatic pigmented macular spots appeared on dorsa of feet. Because of their smoothness, yellowish center, and purplish edges, necrobiosis lipoidica was suspected in 1952 but biopsy sections were not conclusive.

Patient returned to the clinic in January, 1958, because of spreading of lesions on dorsa of feet. Biopsy specimen taken at this time showed typical picture of focal necrobiosis with surrounding histiocytes and lymphocytes and with fat droplets demonstrable in this area.

While five years ago the glucose-tolerance test was borderline normal, now it is definitely diabetic. Urine sugar at the beginning of test was a trace; at one-half hour, a trace; at 2 hours, 4+, and at three hours, 1+; blood sugar, 147 mg. % at time of test, 268 mg. % in one-half hour, 191 mg. % in two hours, and 138 mg. % in three hours.

Discussion

DR. S. J. ZAKON: After Oppenheim and Urbach published their reports on necrobiosis lipoidica diabeticorum in 1932, a number of reports of necrobiosis lipoidica appeared in patients without diabetes. However, Oppenheim always insisted that these patients were potential diabetics and that diabetes would show up at some time.

The case presented by the University of Chicago in 1952 had then a normal blood sugar, while now she is definitely diabetic. If Dr. Marshak will observe her patient long enough, she will find that the patient will probably develop diabetes. Urbach published a paper which was widely discussed, on skin diabetes (1937). Apparently, the concentration of glucose can often be much higher in the skin and may not show up in the blood. This paper was not well accepted because there were many tests which were so difficult to perform that there were many chances of error. I think both cases presented today are classical cases of necrobiosis lipoidica diabeticorum.

DR. THEODORE CORNBLEET: The glucose-tolerance curve here is flat—certainly not normal. Perhaps this presages a rebound effect later. We could not corroborate the late Dr. Urbach's work showing that the skin retains a disproportionate amount of sugar in certain cases, such as in some pyogenic infections. We found the blood and skin sugar levels are in equilibrium. The changes in skin glucose levels parallel, but lag behind, those of the blood 30 to 45 minutes.

DR. STEPHEN ROTHMAN: Dr. Urbach's findings are difficult to discuss because the validity of the available methods for estimation of glucose in skin tissue is debatable. I agree with Dr. Zakon that the reliability of these methods can be seriously criticized, and I am sure Dr. Cornbleet will also agree. In my experience, in chronic furunculosis low-carbohydrate diet (100 gm. daily) is an extremely effective therapeutic measure, and because of this empirical fact, I am inclined to believe that there is something to Urbach's claims that some persons' skin will store sugar more than that of others.

DR. ROTHMAN: The patient presented from our department had no diabetes when first seen in 1952. She had some discoloration on the dorsum of her foot, which histologically was not quite characteristic for necrobiosis, although clinically this possibility was suspected. By now she has a diabetic tolerance curve and the histologic picture of the skin is typical for necrobiosis. In all probability, this diabetes is not of pancreatic but of pituitary origin—as all these obese patients show signs of hyperpituitarism and hypercorticoidism. In many patients with necrobiosis without diabetes family history of diabetes is obtained, and they can be regarded as latent diabetics. I do not agree that 25% of all patients with necrobiosis "have no diabetes." Of course, necrobiosis is not a direct consequence of carbohydrate metabolism disturbance but rather a result of diabetic vascular changes.

Lichen Sclerosus et Atrophicus. Presented by DR. I. MYRON FELSHER and (by invitation) DR. J. HARVEY JOHNSTON.

A 70-year-old white woman was first seen in the office on Jan. 30, 1958, complaining of a "tightness" and dryness of the skin of the breasts and tenderness in the area of the left breast. The disorder began over eight years ago in the left breast and gradually spread, involving the lower

half of the breast and a large area under it. The right breast became affected in the last two years. Only in the last year she noticed the tenderness on the left breast.

The patient is diabetic, requiring 30 units of protamine zinc insulin daily. Recently she had occasional bleeding from the anal area due to a small tumor in that region, for which surgery is planned.

Examination reveals atrophy of the skin of the lower half of the left breast and the adjacent area on the abdomen under it, a smaller, circular area on the dependent portion of the right breast, and a small area on the left perianal region. The affected skin is dry, with a parchment-like or tissue-paper-like wrinkling, glossy, yet rather loose enough to move freely over the underlying structure, and mottled with ivory and brown. In some areas telangiectasis is present.

The blood serologic test was negative, and the blood cell count and urinalysis were within normal limits.

Histopathology: The histologic picture of a biopsy specimen from the left breast shows relative hyperkeratosis, keratotic plugging of the hair follicles, atrophy of the rete malpighi, flattening and loss of the rete ridges, lymphedema in the upper portion of the cutis, with edematous changes in the connective tissue fibers beneath the epidermis, and, finally, a cellular infiltrate in the midcutis beneath the area of edema.

Discussion

DR. MARCUS R. CARO: I do not believe the case should be dropped without discussion, even though I agree with the diagnosis as presented. In a few years these lesions can change their histopathologic appearance to that of morphea. I recall two cases in which I made a diagnosis of lichen sclerosus et atrophicus both clinically and on the sections, and later on they changed into lesions of morphea. I think that the patient should be observed and a year or two from now a repeat biopsy should be performed.

DR. I. MYRON FELSHER: When one sees a cutaneous disorder in a diabetic, he cannot help wondering whether the diabetes had something to do with the disease. In the literature most of the cases described have emphasized that there are no systemic diseases associated with lichen sclerosus et atrophicus. Whenever one looks at the pathology, he finds that lichen sclerosus et atrophicus is not an inflammatory disease. The edema is very marked in the fibrous layer. There is quite a bit of homogenization of the tissue. That type of pathologic change could be induced by some chemical process which could start from a metabolic disturbance, an endocrine distrubance or imbalance of electrolytes. I know, in spite of the fact that other cases described do not have any underlying systemic disease, we could well venture on the speculation that perhaps they had subclinical or minimal clinical factors which could not be measured at clinical level but which could produce certain changes under certain conditions.

Three years ago I presented a middle-aged man with extensive lichen sclerosus et atrophicus. The origin appeared to be an iritis; though he had undergone surgery he remained neurotic. He developed hemorrhagic bullae and became very alarmed. He was put on a nitrogenous diet supplemented by vitamins and given a very bland topical application. He was told not to irritate the lesions. In five months the hemorrhagic bullae had disappeared. I saw him three months ago and found that the lichen sclerosus area had become much smaller. Here again we may speculate that the injured area had some metabolic change which may have induced change in the skin and later on when the error was corrected the same peculiar lesions recurred.

Necrobiosis Lipoidica (Non-Diabetic). Presented by DR. LYDIA C. MARSHAK and (by invitation) DR. BRIAN POTTER.

Squamous Cell Epithelioma. Presented by DR. SAMUEL M. BLUEFARB.

Multiple Keratoses with Associated Epithelioma. Presented by DR. ADOLPH ROSTENBERG JR. and (by invitation) DR. J. M. FOX and DR. R. F. BETTASSO.

Hereditary Hemorrhagic Telangiectasia. Presented by DR. ADOLPH ROSTENBERG JR. and (by invitation) DR. J. M. FOX and DR. LOUIS SCARAMELLA.

Case for Diagnosis: Stasis Dermatitis? Presented by DR. SAMUEL M. BLUEFARB and (by invitation) DR. J. HASEGAWA and DR. F. E. DUNLAP.

Epidermolysis Bullosa. Presented by DR. DAVID COHEN and (by invitation) DR. STUART BACHMAN.

Multiple Glomus Tumors. Presented by DR. ROGER W. PEARSON (by invitation) and DR. BRIAN POTTER (by invitation).

North American Blastomycosis. Presented by DR. STEFAN BIELINSKI.

Bullous Eruption. Presented by DR. MARCUS R. CARO, DR. JOHN B. HAEBERLIN, and (by invitation) DR. ROLAND S. MEDANSKY.

Generalized Trichophyton Rubrum Infection. Presented by DR. IRENE NEUHAUSER.

Koilonychia with Iron Deficiency Anemia Due to Carcinoma of the Urinary Bladder. Presented by DR. SAMUEL M. BLUEFARB, DR. SILAS WALLK, and (by invitation) DR. MARTIN L. GECHT.

Bromoderma. Presented by DR. THEODORE CORNBLEET, DR. SIDNEY BARSKY, and (by invitation) DR. H. YAZDI.

Pseudoxanthoma Elasticum. Presented by DR. SAMUEL M. BLUEFARB, DR. SILAS WALLK, and (by invitation) DR. H. YAZDI.

Arteriosclerotic Ulcer. Presented by DR. JAMES R. WEBSTER, DR. STANLEY HUFF, and (by invitation) DR. H. YAZDI.

Tuberculosis Cutis Colliquativa. Presented by DR. DAVID V. OMENS and (by invitation) DR. HAROLD OMENS and DR. MARTIN L. GECHT.

Sarcoidosis. Presented by DR. SAMUEL M. BLUEFARB and DR. SILAS WALLK and (by invitation) DR. J. LATONI.

LOS ANGELES DERMATOLOGICAL SOCIETY

S. W. Becker, M.D., President
Floralou Kettenbach, M.D., Secretary
March 15, 1958

Lymphoblastoma in Remission; Eosinophilic Granuloma with Eosinophilia? Presented by DR. LAWRENCE M. NELSON.

The patient is a 57-year-old woman teacher.

This patient was presented at the Santa Barbara meeting of the Los Angeles Dermatological Society in 1951. At that time it was the consensus of the discussants that she had lymphoblastoma, type to be determined. Her case was subsequently followed in Los Angeles by several doctors. Dr. Foord, of the Huntingdon Memorial Hospital, felt that she had leukemia, and Dr. Herman Pinkus made a diagnosis of Hodgkin's disease. She continued to have nodules and tumors in spite of taking various steroids. In January, 1953, she had a gastrointestinal upset with a fever (temperature as high as 102 F or 103 F). The tumors started to disappear but subsequently increased somewhat. In early August, 1953, she had another fever, for which she was given oxytetracycline (Terramycin). She apparently had a reaction to the drug. The rest of her tumors subsequently disappeared. She was hospitalized in June, 1955, because of a generalized lichenified, pruritic dermatitis, much like that for which she was originally seen. She was again seen March 20, 1957, when she was in the hospital for a cholecystectomy. At that time she had a scaling, dry dermatitis over the iliac crests, buttocks, and elbows. The course of her eosinophilia and leukocytosis is recorded on the attached chart [Table].

Fig. 1.—Lymphoblastoma? Taken April 3, 1951.

Fig. 2.—Lymphoblastoma? Taken Jan. 29, 1952.

She had intermittent steroids in small doses from 1951 until 1955. Since then she has had sedation and tranquilizers at intervals.

Discussion

DR. LOUIS H. WINER: Although the blood picture is that of lymphatic leukemia and the cytology of the blood smear is that of lymphatic leukemia, the histologic section is too pleomorphic for a diagnosis of lymphatic leukemia. This could be, as I thought at her previous presentation several years ago, a type of myelogenous leukemia. In the sec-

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Summary of Data

Date	RBC	HGB	WBC	Lymph	Eos	Morphology
6/15/51	4,990,000	13.8	52,600	38	53	11% of eos are stab forms; 14% of lymphs are abnormal — rare one shows slight immaturity
11/13/51	5,100,000	14.5	33,800	41	50	8 eos/100 WBC are stab forms
4/18/52	5,390,000	15.3	27,300	28	46	7 eos/100 WBC are stab forms
6/23/53	5,140,000	14.7	24,100	28	47	Rare eo is stab form
8/24/57	5,040,000	14.1	12,800	26	28	One-third eos are stab forms — no younger forms seen
6/16/55	5,170,000	15.6	9,250	14	13	Normal
2/ 7/58	——	12.5	7,050	27	13	Normal

tion there are clear vacuolated cells with round vesicular nuceli which are invading the cutis and pushing aside and causing an absorption of connective tissue. There are also Langhans giant cells present. The foamy structure of the cells suggests xanthoma and mycosis fungoides. In mycosis fungoides we find liquefaction necrosis and degeneration with formation of clear spaces. This sometimes is also seen in xanthomas which have not become fibrotic but are absorbing a great deal of cholesterol.

DR. LAURENCE J. UNDERWOOD: Are the present lesions, which appear to be neurodermatitis, related to her past lymphoblastoma problem or is it a nonspecific and unrelated process?

DR. GORDON MACDONALD: I'm impressed with Dr. Winer's thoughts about mycosis fungoides. I am wondering whether it is not possible that this thing she has now that looks like neurodermatitis (and probably is neurodermatitis) might not be an eczematous phase of mycosis fungoides or some related condition. I wonder if a biopsy might not prove to be interesting.

DR. LAWRENCE M. NELSON: This woman has a neurodermatitis—that's what I saw her for first, years ago, before she developed the great tumors. As a matter of fact, I had biopsies that were taken from these lichenified plaques, but I didn't think they were interesting enough to bring along. I think that the neurodermatitis is unrelated to the tumors—or the lymphoblastoma, as you will. I thought she was my prize patient and was rather disappointed seven years ago when I didn't get more discussion. I haven't seen anything quite so dramatic in my life—I've never seen anything like this regress spontaneously, either. She has had a little steroid—but not for three years. I can't tell you exactly what she's had for treatment, but it certainly hasn't been much. She hasn't had any urethan or nitrogen mustard or any drugs of that group. Maybe I can show her again in eight more years.

Atrophie Blanche en Plaque. Presented by DR. LAWRENCE M. NELSON.

Pustular Aerodermatitis. Presented by DR. LAWRENCE M. NELSON.

JOINT MEETING OF THE LOS ANGELES DERMATOLOGICAL SOCIETY AND THE METROPOLITAN DERMATOLOGICAL SOCIETY OF LOS ANGELES

April 26, 1958

LOS ANGELES DERMATOLOGICAL SOCIETY

S. W. Becker, M.D., President

Floralou Kettenbach, M.D., Secretary

METROPOLITAN DERMATOLOGICAL SOCIETY OF LOS ANGELES

L. J. Underwood, M.D., President

Max Popper, M.D., Secretary

Discoid Lupus Erythematosus: Bilateral Macular Degeneration Due to Chloroquine. Presented by DR. THOMAS H. STERNBERG and DR. EDWARD LADEN.

A 32-year-old Caucasian housewife is presented.

There is no family history of macular disease or other unusual visual difficulties. At the age of 9, she had asthma, probably due to wool and house dust, but she has had no allergic manifestations since that time. She had pneumonia at age 6 and severe sinusitis at the age of 11.

The patient developed severe sunburn in mid-1950 with disproportionate reaction. Following this she felt run down and tired easily. In September, 1951, she developed three skin lesions on her right arm. In December, 1951, she developed more skin lesions on the left side of her neck. In January, 1952, following prolonged sunbathing, she developed additional skin lesions on her face, back, chest, and legs. A biopsy was performed, and a diagnosis of discoid lupus erythematosus was made. The patient was then treated successively with bismuth, gold, and atabrine without much improvement. In July, 1953, she became pregnant, and the skin and general condition improved. Two and one-half weeks post-term, the skin lesions exacerbated.

Patient shows the lesions of discoid lupus erythematosus with residual scarring about the face.

Funduscopic examination reveals bilateral macular degeneration, and the patient has decreased central vision.

Biopsy findings are consistent with discoid lupus erythematosus.

Other Significant Laboratory Findings: Negative L. E.-cell test. Hemoglobin, 15.1 gm. WBC, 9950. Differential count, within normal limits. Urinalysis, within normal limits.

Treatment and Results: In May, 1953, she was started on chloroquine, 250 mg. b. i. d., with definite clinical improvement. In June, 1954 the proximal ½ in. of her hair turned light honey-colored. The chloroquine was stopped at this point, and the L. E. relapsed. The chloroquine was resumed, and

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the patient continued to do well. On Jan. 23, 1958, blurring of vision was noted and the chloroquine was decreased to 1 tablet per day. On Feb. 26, 1958, the chloroquine was stopped entirely. Because of continued blurring of the vision, ophthalmological consultation was obtained in April, 1958. Blurring was found to be due to bilateral macular degeneration. Triamcinolone, 4 mg. q. i. d., was begun on April 4, 1958, with improvement of skin lesions but with no beneficial effect on the visual disturbance to date.

Discussion

DR. A. FLETCHER HALL: Dr. Scholtz had to leave before the beginning of the discussion and asked me to relate the few points that he wished to make. The first one was that *transient* dimming of vision is not unusual with chloroquine but that damage in this case is probably permanent; he feels that there is no evidence that continuous therapy with chloroquine is any more effective than interrupted courses, and, as a matter of fact, most chloroquine reactions are due to an accumulated effect. It was his opinion that continuous administration of chloroquine over a period of about a year as was given in this case is inadvisable. I agree, so far, with the remarks that he wanted me to make. The next remark, with which I don't agree but which I said I would relay to you, is that the treatment of choice of chronic discoid lupus erythematosus is the steroids. The remark which I would like to make, with which he does not agree, is that the treatment of choice of chronic discoid lupus erythematosus is gold sodium thiosulfate intravenously. In my experience, which embraces about 30 years, I have never seen an untoward reaction to gold sodium thiosulfate intravenously in dosage of 50 mg. per week or less. I have never seen any untoward reaction that can compare with even the milder side-reactions to Atabrine, chloroquine, and all of the other drugs of that group. Furthermore, I have never treated a case of chronic discoid lupus erythematosus with one of the Atabrine-chloroquine series without an immediate relapse (I don't mean two months, I mean within a week or two or three) after the drug was discontinued. With gold, of course, we see a relapse. But, in my limited experience, it seems to me, in general, the relapse has not been as quick or as certain as it has been in the cases that I have seen treated with the chloroquine group of drugs. I might also say that the scarring in this case brings up an interesting point regarding treatment, to me, at least; all of the scarring that I can see, without very, very close examination, was scarring that was typical of refrigeration with solid carbon dioxide; the scarring of the lupus erythematosus, untreated by refrigeration, was scarcely visible.

DR. THOMAS H. STERNBERG: I am sorry that some of the information that you should know about this patient is not on the chart. The patient was examined after this second blurring failed to disappear by Dr. Ernest Hillyer, an ophthalmologist, and he found bilateral macular degeneration. He requested that her eyes not be dilated when examined by so many people at this meeting, since he thought it might further damage her retinae. Dr. Hillyer suggested an alternate diagnosis—discoid lupus erythematosus involving the retinae. This is apparently an extremely rare condition if it occurs at all, since a cursory examination of the literature failed to reveal a similar case.

DR. RONALD M. REISNER: In a fairly complete search of the literature I was unable to find any instance of irreversible anatomically demonstrable changes in the retina as a result of chloroquine therapy. The most commonly described visual abnormalities due to chloroquine were blurring of vision and decreased speed of accommodation. These changes, however, were in all cases reversible on discontinuing the drug. It is of interest, however, that some structurally related compounds such as quinine and quinacrine have been shown to produce anatomically demonstrable changes in the retina in isolated cases. Quinine is recorded as producing peripheral visual field defects in most cases and more rarely central visual field defects of the type that this woman had. The two mechanisms which are postulated as responsible are (*1*) a direct toxic effect of quinine on the ganglion cells of the retina and (*2*) an indirect effect mediated through vascular spasm. These visual field defects, however, are usually considered to be reversible and have not been shown in the vast majority of cases to be associated with any anatomically demonstrable changes in the retina. There is one case of retinal damage due to quinine in the literature (*Arch. Int. Med.* 80:763, 1947), that of a merchant seaman who thought he had malaria and treated himself for a period of three years with daily doses of 1 to 3 gm. of quinine. He entered the hospital comatose. Examination of the eyes revealed pale retinae and discs and attenuation of the arterioles which subsequently went on to complete and permanent blindness with atrophy of the optic nerve. Meyler in his "Side Effect of Drugs," in 1952, described the probable mechanism of quinine sensitivity as one of angiospasm. Optochin, a derivative of quinine, has also been known to produce central scotomata but without anatomically demonstrable changes. Finally, quinacrine, or Atabrine, has been recorded as producing permanent blindness in one case (Cole et al., *J. A. M. A.* [Dec. 26] 1953). This case quoted by Cole, however, is from a French ophthalmological bulletin (*Bull. ocul.* [July-Sept.] 1945) which is not locally available, and so we have no further

details. Since the macula and particularly the fovea, the central portion of the macula, is extremely susceptible to ischemia, owing to the nature of its blood supply, it is conceivable that in isolated instances an angiospastic agent could produce permanent damage by this mechanism. This possibility certainly should be considered in this woman. In talking with the ophthalmologists and looking through the literature, I was unable to find a single case of isolated bilateral degeneration of the maculae due to lupus erythematosus. Finally, the possibility of completely unrelated disease such as heredofamilial degeneration of the macula must be considered. However, this woman has absolutely no family history of ocular disease.

DR. MAX POPPER: Because of the potential danger that lies in the treatment of chronic discoid lupus erythematodes with Atabrine or chloroquine, I prefer local treatment alone with carbon dioxide snow, which, in my experience, is very effective. This treatment results in a very smooth and cosmetically acceptable scar in the majority of cases. H. E. Michelson, discussing lupus erythematosus in the *Archives of Dermatology*, a few years ago, also gave preference to this treatment. He states: "Freezing the lesion with solid carbon dioxide is the best local remedy in my experience, and I know of no other method which equals it." "I gave up the use of bismuth and gold salts because the result did not warrant the long-continued use that was necessary to achieve the indifferent results, nor did their use prevent new lesions from occurring." As to the treatment with quinacrine (Atabrine), H. E. Michelson states: "I have not shared the unbounded enthusiasm of some concerning quinacrine. Until a better drug is discovered, I believe it should be tried in the chronic discoid form and in some cases of subacute lupus erythematosus." "Its precise position in the therapy of lupus erythematosus cannot be fixed until it has been in use for at least five years" (*A. M. A. Arch. Dermat. & Syph.* 69:704-705 [June] 1954).

DR. J. WALTER WILSON: There are, of course, individuals who are born with non-functioning maculae of the eyes and they go through life with two very prominent symptoms: one is called hippus, which is an alternating dilation and constriction of the pupil, and the other is a circular nystagmus, manifested by the eyes continually wandering in a sort of circular motion in an attempt to find a spot yielding sharper vision, unsuccessfully, of course, since there are no maculae to focus upon. I would expect that severe toxic damage to the maculae would cause similar behavior. This girl, in just a rough observation, did not present these characteristics. Dr. Sternberg tells me that he has not observed them. I wonder, then, how easily the ophthalmologist can tell what degree of permanent damage she has sustained, since so much would depend on subjective information. I believe that if she had severe damage to the maculae she would show nystagmus.

DR. THOMAS H. STERNBERG: This is a very worrisome patient, since it is probable that the retinal damage and loss of vision is permanent and since it eliminates the further use of the drugs which have been helpful in this case. Dr. Hillyer felt that her eyes might show some improvement from steroids, but this was not the case.

Primary Inoculation Coccidioidomycosis. Presented by DR. EDWIN T. WRIGHT, DR. VICTOR D. NEWCOMER, and (by invitation) DR. NORMAN H. NELSON.

A 34-year-old Japanese (Hawaiian) man is a laboratory technician.

The family history is noncontributory.

The patient first began working with cultures of Coccidioidomycosis immitis in October, 1957. At this time his coccidioidin skin test was negative. Chest x-ray was negative, and to the best of his knowledge he had had no prior contact with this organism nor had he resided in an endemic area.

On Dec. 18, 1957, the patient traumatized the tip of the left index finger with a hypodermic needle contaminated with an experimental culture tissue phase of C. immitis. No local or systemic disease followed this inoculation. On Jan. 13, 1958, the left index finger was again accidentally inoculated with the same material, and the patient was admitted to the Veterans Administration Hospital on Jan. 22, 1958, complaining of a persistent erosion on the tip of the left index finger associated with fever, malaise, and epitrochlear and axillary soreness of two days' duration.

The patient presented an essentially asymptomatic, shallow, crusted erosion about 0.5 cm. in diameter on the end of the left index finger which was surrounded by a violaceous discoloration encompassing the lateral aspect of the terminal phalanx. A mass 3 cm. of diameter was palpable in the left epitrochlear area. Palpation of the left axilla revealed tenderness but no definite adenopathy. Oral temperature was 101 F.

Other significant physical findings: None.

Other laboratory work: Admission CBC, urinalysis, and chest x-ray were within normal limits. Sedimentation rate was never elevated above 9 mm. in an hour on repeated testing. Repeated cultures of lesion on left index finger were positive for C. immitis.

Skin testing: Coccidioidin 1-100, 4+; 1-1000, 2+; blastomycin 1-100, negative. Histoplasmin 1-100, negative; PPD No. 2, 2+.

Complement-fixation tests: The initial and repeated tests at weekly intervals have been negative-to-positive in 1:2 dilution. This was not considered

to be significant by Dr. C. E. Smith, University of California, Berkeley.

Precipitin tests: These were negative until Feb. 4, 1958, when they gradually increased in titer to 4+ in 1:10 dilution.

Biopsy findings (Jan. 23, 1958): Left index finger: A marked granulomatous reaction is seen throughout the dermis. A number of spherules containing endospores are present.

Treatment and Results: Patient has received no specific therapy. The lesion on the finger tip has resolved about 50%, and the epitrochlear mass has decreased in size. A persistent nodule is present on the dorsum of the left hand, and the patient has a few small nodes in the left axilla. The last three cultures from the finger tip have been negative for C. immitis.

Discussion

DR. J. WALTER WILSON: In 1953 we reported the first instance of a person who had been inoculated intracutaneously with coccidioides. He developed a lesion which was entirely like sporotrichosis when inoculated in the same manner, including lymphadenopathy and lymphangiitis in the region draining that area and several nodules scattered along the vessels. A second instance occurred in a person who worked in Dr. Conant's laboratory in Duke University about four years ago. Those two persons became completely well and have shown no signs of recurrence. This occurred, of course, without any specific therapy, because nothing which could be called specific was available in those days. We believe that this type should not desseminate in any higher percentage than if the disease were to be acquired in the common manner, that is by inhalation, perhaps only once in a thousand instances.

The present case is identical to these two, except that the patient is dark-skinned and we know that persons with pigmented skins do not resist this disease so well. However, thus far we have some good evidence that he is fighting the infection in a normal, successful manner. He has had a highly positive reaction to the skin test with coccidioidin, in the standard dilution of 1:100. I think we can even assume that he didn't actually become infected with the organism the first time his finger was inoculated, because the precipitin test did not begin to be positive until Feb. 4, which was almost a month after the second inoculation, and that test usually becomes positive very early in the course of the disease. So, if he had successfully inoculated himself in December, he should have had a positive precipitin test when first examined. The complement-fixation test, in his case, has stayed low—1:2 being the highest positive dilution recorded so far. This is in favor of a very small amount of infection being present at the time the test is made. The other two cases on which we base our conclusions also failed to show complement-fixation tests in any high titer, only 1:2 or 1:4 dilutions.

There are a couple of other interesting observations today. I took a culture from a droplet of pus which came from a spot over one of the lymphatics in this man's axilla five days ago. Also, I diluted a drop of the purulent material with saline on a slide and rimmed the edges of the coverslip with petrolatum. This is a very easy way to make the diagnosis conclusively of coccidioidomycosis within 24 hours if you have been lucky enough to get some pus. At once the organisms begin to germinate, forming several hyphae from each, and they are easily discovered and identified 24 to 48 hours later. In 2 drops of purulent material, there were only 4 viable, germinating organisms.

DR. LOUIS H. WINER: Even though the inoculation site improved very rapidly with moist applications, lymphangiitis and a deep tender nodule developed on the forearm. Specimens which were removed for biopsy from the primary site, as well as the forearm nodule, show sporangia with endospores. The section of the nodule from the forearm shows that it is a granuloma in the subcutaneous fat in which a vessel shows invasion with a large spore full of endospores. Because of this vascular invasion, in spite of past reports of cases of primary-inoculation coccidioidomycosis recovering, I believe this patient has a poor prognosis. This is borne out by more recent development of deep axillary lesions from which coccidioidomyces immitis has been cultured.

DR. J. WALTER WILSON: This man, so far, has not had the disease for the same number of months that the other two persons who preceded him had it—to show whether or not he will follow the course to complete healing. If amphotericin is given to him now, it might receive credit for another "cure" that it doesn't deserve. Therefore, I would rather wait for at least two or three months and see if he doesn't heal spontaneously. If he doesn't at that time, I will bow and let him be given amphotericin.

DR. NORMAN E. LEVAN: This clear-cut instance of primary cutaneous coccidioidomycosis raises important points concerning the pathogenesis, prognosis, and chemotherapy of the disease—matters of more than academic interest to clinicians in endemic areas. With some species variations, coccidioidomycosis runs similar courses in many mammalian species. For example, primary pulmonary infections are usual in naturally occurring cases of animals as well as man and may be similarly self-limiting (Levan, N. E., and Burger, C. H.

California Med. 83:379, 1955). It could be anticipated that the tissue phase of C. immitis when introduced into the skin would prove as pathogenic for human beings as it commonly does for laboratory animals. Further, since cutaneous inoculation in animals may be followed by dissemination, the same may be true in a human case, but, by analogy with primary pulmonary infections, such failure of the immune mechanism should occur very infrequently. The persistent essentially negative complement-fixation reaction is strong evidence that this patient has his infection under control. While weak or negative reactions occur at times in the face of disseminate disease, it is usually where this dissemination is limited to an occasional small granuloma; the test may thus reflect the amount of infected tissue as well as the allergic/immunologic status. On the other hand, I found clinical evidence suggesting dissemination already present in this case: a granulomatous 3 mm. skin lesion which the patient states has appeared in the past few days, adjacent to the left axilla with its infected nodes. Should the disease disseminate, the prognosis, while grave, is still not hopeless. Disseminate coccidioidomycosis runs the gamut from minute solitary cutaneous granulomas to rapidly fatal meningitis. It should be generally understood that at least half the patients with the disseminate cases do not succumb to their disease; I have presented numbers of self-limited *untreated* instances before this society. Unfortunately, it has been a common error to assume that improvement or survival of cases receiving some drug or vaccine must be due to such treatment. At the present time there is no demonstrably effective agent. I would strongly recommend that testing of drugs be carried on only in scientific controlled fashion and not in desultory and uncontrolled clinical trials. A possible exception is the use of drugs in the almost invariably fatal meningitis cases.

DR. NORMAN H. NELSON: I would like to thank the discussors for their highly interesting comments on this case. This patient fulfills eight of the criteria that have been set forth by Dr. Wilson and associates in *California Medicine*, Vol. 79, September, 1953. Therapy with the newer antifungal drugs was withheld because Dr. Wright and I are of the opinion that this patient will fulfill the ninth criterion—that of spontaneous healing of the cutaneous syndrome—within a period of months.

Lichen Planus. Presented by DR. THOMAS H. STERNBERG.

The patient is a 20-month-old female Caucasian who has previously been presented before both the Metropolitan and Los Angeles Dermatological Societies, with the diagnosis of lichen planus and poikiloderma congenitale entertained.

The parents first noted sharply demarcated erythema of cheeks soon after the baby switched from breast to homogenized milk at the age of 2 to 3 months. There ensued gradual spread of the eruption to the knees, extensors of the forearm, and the wrist. The baby was placed on a restricted diet without any benefit. Local cortisone was followed by increased pigmentation at borders of the lesions. Her mother noted definite aggravation by sun exposure. The eruption continued to spread to involve the face, hands, legs, and buttocks.

On hospitalization on Dec. 3, 1957, the patient showed sharply demarcated plaques with peripheral hyperpigmentation, erythema, central atrophy, and reticulated pigmentation over the face, arms, legs, and buttocks. The remainder of the physical examination was within normal limits. Since that time the lesions have cleared, and show only residual pigmentation.

Biopsy findings: 1. Dr. Hamilton Montgomery—consistent with lichen planus.

2. Dec. 4, 1957, specimen removed from the right thigh—suggestive of lichen planus and poikiloderma congenitale.

Other significant laboratory findings (abnormal and normal): CBC and urinalysis within normal limits. Serum vitamin A level within normal limits. VDRL—negative. Chest x-ray—within normal limits. X-rays of long bones within normal limits. Coccidioidin, histoplasmin, and tuberculin skin tests—negative.

Treatment and results: After hospitalization and discontinuation of a vitamin mixture, the lesions began to clear. On Dec. 17, 1957, triamcinolone, 1 mg. q. i. d., was begun. Increased to 6 mg. q. d. Slow improvement ensued. On Feb. 7, 1958, triamcinolone was discontinued and bismuth subsalicylate 0.2 gm. i. m. each week was begun, with subsequent marked improvement. For the past several weeks the eruption has been completely healed and the residual hyperpigmentation is fading.

Discussion

DR. S. WILLIAM BECKER: We presented a girl sometime ago before this society, who had, I think, typical Thomson's poikiloderma. She presented atrophic macules, telangiectasia, and hyperpigmentation. She had little bony abnormality. The sections looked a little bit like lichen planus, but I think the infiltrate extended more deeply than one usually sees. There was no parakeratosis which goes along with lichen planus. However, as Dr. Newman said, the atrophy that this child presents is punctate, with small atrophic lesions here and there. There are certain conditions which have been reported from time to time as lichenoid eruptions which are followed by hyperpigmentation

(I remember seeing one in London) which may eventually change to mycosis fungoides, but I don't think that occurs in a child of this age. I question whether this is the real Thomson's poikiloderma, but I believe it is a lichenoid eruption which is followed by hyperpigmentation, perhaps a lichenoid drug eruption which might leave pigmented plaques similar to these.

DR. LOUIS H. WINER: The histologic section shows no changes in the epidermis. There are melanin-bearing histiocytes and a perivascular infiltration of lymphocytes and eosinophils surrounding the superficial vessels which are involved by endothelial proliferation. My diagnosis is drug eruption with postinflammatory melanosis.

DR. THOMAS H. STERNBERG: This patient has been previously presented at both the Los Angeles Dermatological Society and the Metropolitan Dermatological Society during the past year. At the time I first saw her, most of the activity was in the borders of the lesions, which were palpable and raised and scaly. The eruption was a large, plaque-like affair, spreading peripherally, and had annular borders. We had the patient here in the hospital and did the usual bone studies for poikiloderma congenitale and didn't find anything. The child is very healthy and is growing normally. We went through the history thoroughly, and the only thing that could be found was that the mother had been giving her a vitamin mixture since birth. It was one of these liquid mixtures containing minerals, including iodine. This was discontinued and triamcinolone therapy was instituted. On fairly small doses, the child did start improving slowly. We then put her on bismuth i. m., and the eruption really melted. The residual pigment is now fading. It seems that we should then abandon poikiloderma congenitale as a diagnosis and consider that this is probably a lichen-planus-like drug eruption.

Lupus Vulgaris. Presented by DR. EDWIN T. WRIGHT, and (by invitation) DR. MICHAEL L. MATTE.

Dermatitis Medicamentosis Due to Phenolphthalein? Parapsoriasis en Plaque (Premycotic Mycosis Fungoides)? Presented by DR. J. WALTER WILSON and DR. PAUL LEVAN.

Darier's Disease Limited to Scalp and Possibly Involving Oral Mucosa Versus Chronic Familial Benign Pemphigus. Presented by DR. HAROLD PRICE.

Lymphoma. Presented by DR. VICTOR D. NEWCOMER, and (by invitation) DR. MORGAN LINDBERG.

Severe Vasomotor Instability. Presented by DR. IRWIN H. LINDEN.

Systemic Lupus Erythematosus: A Therapeutic Problem. Presented by DR. VICTOR D. NEWCOMER, and (by invitation) DR. RONALD M. REISNER.

Benign Lymphocytoma Cutis? Presented by DR. THOMAS STERNBERG; DR. LOUIS H. WINER, and (by invitation) DR. PAUL J. GETHNER.

THE METROPOLITAN DERMATOLOGICAL SOCIETY OF LOS ANGELES

Laurence J. Underwood, M.D., President
Eliot Wolk, M.D., Vice-President
Max Popper, M.D., Secretary
Feb. 25, 1958

Linear Lichen Planus. Presented by DR. EDWARD L. MURPHY.

A 44-year-old white man presents a pruritic linear eruption, ½ to 1 in. wide, extending from the sacrosciatic notch to the right heel. The lesion consists of discrete and confluent violaceous papules with a thin glistening scale.

It has been unchanged since inception, for approximately four months.

There are no other lesions.

Biopsy report has not yet been received.

Discussion

DR. WILLIAM B. REED: I suggest that this may be lichen striatus. The important thing for proper diagnosis is the biopsy. Lichen striatus by biopsy shows an eczematous picture.

DR. HAROLD C. FISHMAN: I would like to support Dr. Reed. I have never seen lichen planus come on like this in a linear fashion. This looks, morphologically, like a nevus unius lateralis. But the history: the first onset of the lesions four months ago, rapidly developing to the present stage and now disappearing, is classical for lichen striatus. Without treatment, it should clear within three or four months.

DR. JOHN W. CARNEY: I am in accord with Dr. Murphy's diagnosis. This patient not only has hard, raised, papular lesions but also in some areas there is actually infiltration and induration of the skin. I don't think you will find lichen striatus with lesions of this description.

DR. EDWARD L. MURPHY: I thought it was a rather striking lichen planus—typical geometric papules, thin-scaled and violaceous coloring, plus the fact that it developed within one week to a full-blown eruption. I don't think lichen striatus would follow the course of the sciatic nerve very closely.

[ADDENDUM: Biopsy report from DR. WILBERT SACHS. Microscopic diagnosis: lichen planus.

We are considering investigating this case from a virus standpoint.]

Submitted for publication May 1, 1958.

Syringocystadenoma Papilliferum Simulating an Angioma. Presented by Dr. Laurence J. Underwood and Dr. Walter S. Green.

A 60-year-old Caucasian woman has had an asymptomatic lesion at the frontal hairline for many years. During the past year it has become elevated. It has "drained fluid" only once "years ago" and never bleeds.

A 1.5 cm. boggy, soft, elevated bluish tumor is located at the hair line. It appeared angiomatous, and when the biopsy was performed a yellowish thin fluid exuded and the tumor collapsed completely, leaving a depression below the surrounding skin.

Kodachrome of tumor before biopsy is presented.

Pathology: The epidermis is not acanthotic but reveals loss of rete pegs. There are some fragments of hair follicles and collections of free-lying erythrocytes in the upper cutis along with mild vascularity and mild nonspecific infiltrate. The *interesting* findings are some large cystic spaces lined by tall columnar cells which appear to be of sweat duct origin. In a few places some villous processes of similar cells may be noted. Also in areas the cells lining the cavity are cuboidal rather than columnar.

Therapy: None. Excision has been recommended.

Discussion

Dr. Harold C. Fishman: (Slide) The slide doesn't show all the features that I would like to see. I would like to see more villi inside of the central area, and I believe that more sections might show it. The actual character of it suggests a sweat-gland type of tumor. Clinically, it is described as a mulberry type of tumor, and this is as classical a picture as I have ever seen. I accept the diagnosis.

Dr. Laurence J. Underwood: One is impressed by the violaceous color of this tumor, and I expected, when I performed the biopsy, to see blood exude rather than the copious straw-colored fluid, followed by immediate collapse of the tumor. I cannot account for the color. This tumor is not a hydrocystoma or hydroadenoma. The area will be excised, saving the specimen for further microscopic study because of the unusual clinical features.

Dystrophic Epidermolysis Bullosa Treated with Chloroquine. Presented by Dr. Clete S. Dorsey.

The patient is a frail-looking 14-year-old boy weighing 109 lb.

His birth weight was 3 lb. 3 oz., but the gestational period was normal. He was kept in an incubator until he weighed 5 lb. At the age of 2 months he developed blisters between his toes. Since that time he has not been free of them. They develop only on the feet, shins and knees, fingers, hands, wrists, and elbows. None have ever appeared in the mouth. There is a definite correlation between trauma and the formation of blisters.

Chronically blistered areas remain scarred and atrophic, but there is no deformity of the digits. There are numerous milia on the dorsum of both hands.

There are no other obvious congenital deformities present. There is no familial history of a similar condition.

The boy attends school but is two grades behind the norm. He engages in mild physical activity.

Chloroquine, 250 mg. per day for 21 days, was prescribed at the time of the first visit. During the first two weeks of treatment blisters formed in the dystrophic areas and the patient complained of aching in muscles and joints. After this initially adverse reaction, he noticed that the tendency to form blisters diminished and for the past 10 days his skin has been in better condition than it has ever been before.

Discussion

Dr. William B. Reed: This patient has the dystrophic type of epidermolysis bullosa. There is no family history of epidermolysis bullosa. Evidently there is a family history of first cousins with fragile bones. This child does not show as marked dystrophic changes as is seen in many of these patients. Many of us have seen the two brothers from North Dakota with actual loss of their fingers. One of them had a fungating granulomatous lesion which proved to be a squamous-cell carcinoma (A. M. A. Arch. Dermat. 75:773 [May] 1957). H. Enell et al. have been reporting on these patients because in some of the isolated communities in Sweden whole families are afflicted with this condition (*Acta dermat.-venereol.* 34:463, 1954). It seems that the simple type is more or less dominant. The dystrophic type is recessive but may be dominant. In regard to therapy, I have never heard of Aralen being used for this condition. Treatment has not yet been found which is successful.

Dr. Clete S. Dorsey: In this case three events were of interest to me: First, all dystrophic areas flared into blisters during the first two weeks of Aralen treatment; second, although Aralen was continued they subsequently improved to a better state than during the previous 10 years; third, between last night and tonight all of the dystrophic areas changed from a state of complete healing to severe blistering (the patient had been off Aralen for one week). This sequence of events raises several questions. Why did the Aralen cause the dystrophic areas to blister? Also, why was this reaction followed by dramatic improvement? And, finally, why, after the patient had been off Aralen

for a week, did the dystrophic areas severely blister within a period of a few hours? Here is blistering without trauma, in a disease which is supposed to blister only as a reaction to trauma. In our present state of knowledge we cannot answer these questions. It is obvious that, in this patient at least, Aralen has a definite effect on epidermolysis bullosa. I shall administer the drug again to see what effect it has over a longer period of time.

Hyperpigmentation of Face: 1. Benoquin-Induced; 2. Dermatitis-Induced? Is This Showing Signs of Leukoderma? Presented by DR. ROSE B. SAPERSTEIN.

PHILADELPHIA DERMATOLOGICAL SOCIETY

James M. Flood, M.D., Chairman
Herbert A. Luscombe, M.D., Secretary
Feb. 21, 1958

Letterer-Siwe's Disease (Reticuloendotheliosis). Presented by DR. IRVING J. WOLMAN (by invitation).

A white boy, aged 4 years, presented a persistent cutaneous rash and crusted lesions on the scalp. The first symptom was pallor, noted at the age of 17 months. At the same time, seborrhea, rash, and "external otitis" began. At 20 months the child developed swelling of the axillary lymph nodes. Medical examination revealed many areas of bone decalcification; their progress has been arrested by local radiotherapy. The patient's nutrition is good so long as adrenal steroids are given. Early blood cell counts ranged from 9.0 to 12.0 gm. hemoglobin, 10,000 to 15,000 leukocytes; 60% to 75% polymorphonuclear leukocytes; no eosinophilia; no abnormal cells.

The report on a biopsy specimen from an axillary lymph node was "reticuloendotheliosis." The report on a specimen from the skin was as follows: "Many histiocytes in subepidermal tissues; these had oval nuclei and pale-staining cytoplasm, often vacuolated. Diagnosis: Letterer-Siwe's disease."

The patient has been treated with steroids.

Discussion

DR. IRVING J. WOLMAN (by invitation): Reticuloendotheliosis is not such a rare condition but that most of you have seen cases of this sort before. Actually, the skin manifestations are a very minor part of the problem of management of these cases. The disease is a general one. Frequently, however, the first manifestation is in the skin as a peculiar form of chronic seborrheic dermatitis. The characteristic endothelial cell of the disease is large, generally 20μ long, with a deep-staining round or oval nucleus. The cytoplasm is pale-staining and very finely granular. The disease is seen at all pediatric ages, and I understand that a few cases have first become apparent in adult life. The disease is nearly always fatal. The rapidity of the course after the onset of symptoms is roughly proportional to the age at onset; when it begins in early infancy, it runs a rather rapid course. This boy at 17 months of age had skin lesions, large axillary lymph nodes, and normal skeletal x-rays. The nodes subsided under x-ray treatment; and in general we turn on the x-rays whenever there is a local area that needs to be treated. At 2 years of age, the prominent complaint was recurrent external otitis. The canals were full of material, and it was clear that the child had infiltration in the walls of both ears, as shown by biopsy from one side. Roentgenogram of the left mastoid showed some bone destruction, and three months later, involvement of the right side. Both lesions improved considerably after x-ray therapy. However, the patient had been losing weight because of poor appetite. Cortisone was then given empirically, because it has been observed that cortisone very often helps these cases. The patient gained weight and strength and became normal in behavior. After a few months, cortisone was stopped for a period of six weeks. During this time the child lost 5 lb., became cachectic, and complained of bone pains when he was picked up. Roentgenograms at this time showed destructive lesions scattered through his vertebrae. Cortisone was started again and in two or three days the symptoms disappeared, and in a few weeks he regained the 5 lb. he had lost. With it all, he has not had any splenomegaly. The liver is palpable; his superficial glands come and go. The most troublesome problem, from the parents' standpoint, is the scalp. He has chronic crusted lesions which have not responded to local treatment. I believe the reason is that the crusts overlie infiltrations in the skin. This boy is unusual because, if he followed a typical course, he should not have survived this length of time. Reticuloendotheliosis is, in general, a steadily progressive disease, with death usually occurring six months to a year after the onset of symptoms. We believe that it is the cortisone therapy which has helped this boy.

DR. H. H. PERLMAN: I have seen about half a dozen cases of Letterer-Siwe's disease, cases in the 6, 8, or 10-year-old group, and one thing that

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strikes me is the marked seborrheic character which they all have. I should like to ask Dr. Wolman and Dr. Beerman whether, in their experience, the histopathologic picture shows the brunt of the situation to fall more on the sebaceous glands than on other structures, in the disease. So far as therapy is concerned, there is not anything I know of that works. We have treated the seborrhea with many things and got nowhere at all. I think it is well for pediatricians to keep the seborrheic element in mind, because it is one of the classical signs of the disease.

DR. HERMAN BEERMAN: I should like to answer Dr. Perlman by stating that in my experience with a few patients, the infiltration and the phenomena in the skin were not at all related to the sebaceous or hair apparatus. I think the trouble with this disease and seborrhea is that its resemblance to seborrhea makes us forget that the patient may have Letterer-Siwe's disease in the beginning. I think Dr. Pastras should tell us of a patient we studied recently.

DR. THOMAS PASTRAS (Collingswood, N. J.): We had a patient at the Graduate Hospital about a year ago, a little girl aged 6, who was in the hospital at age 3 for biopsy of a thyroid nodule, the histologic report of which was malignancy of the thyroid gland. The entire mass was excised, and the area was irradiated. It was predicted that this child would be dead within one to three years. Three years later we saw the child with a typical picture of Letterer-Siwe's disease, and after multiple biopsies we finally proved the diagnosis with a histologic picture similar to that discussed tonight. With the use of steroid drugs, the child is still living and is improving—a total of four years with the disease. The point to be made is that this disease in its early stages may not be characteristic at all, but may present itself in abortive or masked form as demonstrated in this case—the diagnosis being entertained only with the passage of time and the development of the "typical" picture.

DR. HERMAN M. PANZER: Because of the intercurrent infection, I thought that there may be a lowered γ-globulin. Is that so?

DR. IRVING J. WOLMAN (by invitation): To my knowledge, the γ-globulin level remains normal. Affected children are not particularly prone to infections apart from areas which are involved.

DR. JOHN E. GERMAN (Reading, Pa.): Inasmuch as this child has responded to x-ray elsewhere and his scalp is severely involved with the same process, a trial of superficial x-ray to this area should be considered.

DR. ALBERT M. KLIGMAN: This child presented exophthalmos of a very marked degree, and it would appear that there is a suggestion of Hand-Schüller-Christian syndrome there, too.

DR. IRVING J. WOLMAN: There is exophthalmos clinically in Hand-Schüller-Christian disease and sometimes in Letterer-Siwe's disease. It is mostly the histopathology of the cells that makes me feel that these are two distinct disorders. The whole cycle of progress in Hand-Schüller-Christian disease tends to be self-limited in that the lesions run a regular course and then heal of their own accord.

DR. ALBERT M. KLIGMAN: There is no typical cutaneous expression of Letterer-Siwe's disease. A goodly number of these cases develop purpuric, psoriasis-like or seborrheic-like plaques on the trunk, and this may be a clue.

DR. MEYER L. NIEDELMAN: At St. Christopher's Hospital for children, I have seen several infants and children in whom the first sign was a seborrheic type of eruption beginning on the scalp. After the child develops pustular lesions, or urticarial lesions with lymphadenopathy and a low hemoglobin, then you lean toward a possible diagnosis of Letterer-Siwe's disease.

Lichen Planus Hypertrophicus. Presented by DR. MEYER L. NIEDELMAN.

A white woman, aged 34, markedly underweight, presented numerous lesions, varying in size from a pinpoint to 3 or 4 in. in diameter. Many of them, on the extensor surfaces of the forearms and legs, were hard, slightly elevated, and verrucous. The color varied from an erythema to deep violaceous. The lesions had a firm scale, difficult to remove, and felt verrucous to the touch. There were large, confluent, atrophic patches in the posterior area of the arms and the left hip. The borders were atrophic. There were numerous areas of atrophy in addition to these lesions. On the "V" of the neck were many atrophic scars and leukoderma, the remains of former lesions. There were numerous areas of macular atrophy, and areas of cutis marmorata on the arms and legs. The eruption began in the summer of 1953, in the upper arms. The lesions gradually spread to the other involved areas. The itching at that time was intense and kept her awake at night. She still gets attacks of itching, but she has never had any blisters. She sunburns very easily. She has never had any lesions in the scalp, elbows, or knees.

The patient stated that she never feels well and is always tired; otherwise the medical examination was negative.

A blood cell count, urinalysis, blood sugar, and blood sedimentation rate were normal.

The report on the biopsy specimen was as follows: "The surface epithelium showed marked acanthosis and marked hyperkeratosis. The granular layer was present in most areas and exaggerated in some. Acanthosis had resulted in elongation and thickening of some of the rete pegs. There was no parakeratosis. In the papillary layer were found dilated capillaries and a moderate

round cell exudate which was principally confined to the papillary layer itself. The connective tissue of the superficial corium appeared more dense and compact in some areas. Very little of the deeper corium was included in the specimen. The findings seem to be compatible with a lichen simplex chronicus or a lichen planus hypertrophicus. Diagnosis: Lichen planus hypertrophicus."

The patient has been treated with chloroquine (Aralen) without benefit. (She has been very irregular in keeping her appointments.)

Discussion

DR. JOHN P. SCULLY (Reading, Pa.): I should like to offer a coincident diagnosis of lupus erythematosus. I think it is possible that she could have both lichen planus and lupus erythematosus. Certainly the distribution and the scarring look very much like lupus erythematosus.

DR. JOHN F. WILSON: I saw this patient some time ago, at which time she presented a butterfly distribution of the eruption on the face. There is not a great deal of atrophy remaining now, but I removed a portion of tissue from the arm, and it presented a rather typical appearance of lupus erythematosus of the chronic discoid type. With chloroquine there was prompt improvement in a short time, and, as the facial lesions had not been present very long, this would account for the slight atrophy shown on the face.

DR. MEYER L. NIEDELMAN: The diagnosis as presented is in keeping with all the clinical and histological evidence. A diagnosis of lupus erythematosus is untenable. When I first saw the patient I thought of psoriasis, lupus erythematosus, and verrucous lichen planus. Three biopsies were all reported as showing hypertrophic or verrucous lichen planus. Aralen and Atabrine had no effect on the eruption. Certainly if she had lupus erythematosus on her face, as stated, we should expect some scarring. There is no scarring whatsoever to-night.

DR. HERMAN BEERMAN: I called this case lupus erythematosus clinically, but it is lichen planus histologically.

DR. JOHN P. SCULLY (Reading, Pa.): I do not see why Dr. Niedelman has to close his mind to the possibility of lupus erythematosus superimposed upon the lichen planus in the background. Why cannot he compass both ideas?

DR. MEYER L. NIEDELMAN: I saw nothing on which to base a diagnosis of lupus erythematosus. She has no follicular plugging and has had such intense itching that it has kept her awake at night. I have never seen a patient with lupus erythematosus with pruritus so severe that she could not sleep at night. I certainly cannot explain that on any other basis than lichen planus. I agree that when I first saw her I thought it lupus erythematosus, and we discussed it, and the conclusion was that this is a verrucous type of lichen planus.

DR. JOHN F. WILSON: This patient shows definite atrophy suggestive of lupus erythematosus.

DR. MEYER L. NIEDELMAN: When lichen planus verrucosus undergoes involution, it leaves these depressed scars. She has numerous atrophic scars in the neck.

DR. JOHN F. WILSON: Lupus erythematosus does likewise.

DR. JOHN P. SCULLY (Reading, Pa.): Deep x-ray in lupus erythematosus will give good results. How can you explain that?

DR. BENJAMIN F. GROSS: It is possible that she might have a lichen-planus-like eruption from the quinacrine (Atabrine).

Angiokeratoma Corporis Diffusum (Fabry). Presented by CAPT. JAMES H. LOCKWOOD (MC), U. S. N.

A white man aged 20, fairly well developed, thin, in no acute distress, presented on the penis and scrotum discrete vascular papules, some with overlying scale. On the lower portion of the anterior chest, abdomen, gluteal areas, and thighs were erythematous macules and papules, a few of which were slightly keratotic. These lesions partially faded on diascopic pressure. In addition, there were present large areas of telangiectasia on both anterior axillary folds. About five months ago the patient noted red macules on his penis and scrotum. Two months ago these lesions became papular and darker red in color. In addition, he has noted new lesions on the abdomen and thighs. The lesions have been entirely asymptomatic. There has been minimal bleeding following trauma to the lesions. The patient states that he has had minimal swelling of both ankles for the past several months, associated with some pain.

Medical examination disclosed no significant abnormalities. The blood pressure was normal.

A complete blood count revealed 12.5 gm. hemoglobin; 4,200,000 erythrocytes; 9350 leukocytes, and a normal differential count; 235,000 platelets, bleeding time 2 minutes 40 seconds; coagulation time, 3 minutes 10 seconds; total protein, 7.15 gm.; albumin, 4.1 gm.; globulin, 3.05 gm.; total cholesterol, 171 mg. %; VDRL, negative.

Roentgenograms of the chest and long bones were negative.

The reports on biopsy specimens of two lesions from the scrotum stated that the lesions were compatible with angiokeratoma.

Discussion

CAPT. JAMES H. LOCKWOOD (MC), U. S. N.: I feel that this is one of those rare cases of

angiokeratoma corporis diffusum universale. There have been only about 25 such cases reported in the literature, mainly from northern Europe and Scandinavia. All the cases reported have been in men and usually occur prepubertally, although there have been a few cases reported shortly after puberty. The localization is very characteristic—penis, scrotum, umbilicus, and buttocks. The patients go on to develop such symptoms as edema, swelling, and pain of the ankles; temperature changes bother them, and as they gradually progress they develop a cardiorenal syndrome with possible enlargement of the left ventricle and hypertension. They often die of uremia. We saw one case at a meeting on the West Coast in a female, not as yet reported, as far as I know. No other cases have been reported in females. It is considered to be a lipid storage disease. Further studies should be done with this in mind, as we expect to do with this patient. We hope to do studies of the muscular wall of the deeper vessels at the site of a lesion because of the report of vacuolated muscle cells which are said to contain the lipid, diaminophosphatide, supposedly related to sphingomyelin. Histologically, the cutaneous lesions may show a superficial portion which is characteristic of angiokeratoma and a deeper portion in which the pathologic change appears to occur in the muscle wall of the vessels.

Epidermolysis Bullosa Hereditaria. Presented by Dr. H. H. Perlman and (by invitation) Dr. Amir Mehregan.

Hydroa Aestivale. Presented by Dr. H. H. Perlman and (by invitation) Dr. Young Pyo Kim.

Lymphangioma. Presented by Dr. H. H. Perlman and (by invitation) Dr. Young Pyo Kim.

Lichen Scrofulosorum. Presented by Dr. Louis D. Hoffstein and (by invitation) Dr. Sompong Tantisira.

Mycosis Fungoides. Presented by Dr. Meyer L. Niedelman.

Mycosis Fungoid Plaque and Tumor Stage. Presented by Dr. Meyer L. Niedelman and (by invitation) Dr. Amir Mehregan.

Striae. Presented by Dr. Meyer L. Niedelman and (by invitation) Dr. Sompong Tantisira.

Parapsoriasis. Presented by Dr. Carroll S. Wright and Dr. Meyer L. Niedelman.

Parapsoriasis, Guttate Variety. Presented by Dr. Joseph K. Corson.

Psoriasis. Presented by Dr. H. H. Perlman and (by invitation) Dr. Sompong Tantisira.

Pityriasis Rubra Pilaris. Presented by Dr. Louis D. Hoffstein.

Seborrheic Keratosis, Generalized Papillomatosis, Dermatosis Papulosus Nigra. Presented by Dr. Meyer L. Niedelman and (by invitation) Dr. Young Pyo Kim.

Primary and Secondary Syphilis (Probably Reinfection). Presented by Dr. Meyer L. Niedelman and (by invitation) Dr. Joseph Hau.

Xanthoma. Presented by Dr. H. H. Perlman and (by invitation) Dr. Amir Mehregan.

Monilethrix. Presented by Dr. Donald N. Tschan.

Urticaria Pigmentosa. Presented by Dr. H. H. Perlman and (by invitation) Dr. Amir Mehregan.

Nodular Vasculitis with Subcutaneous Fat Necrosis, Cause Undetermined. (2) Chondrodermatitis Nodularis Helicis. Presented by Dr. John P. Scully (Reading, Pa.).

Sjogren's Syndrome. Presented in April, 1957, by Dr. John P. Scully (Reading, Pa.).

The New, Newer, and Newest

It seemed such a harsh order for a mild attack—"Six weeks in the hospital for the coronaries to heal and six more at home in intelligent convalescence." But the time passed quickly and not unpleasantly what with the kindness and concern of associates and colleagues, the encouraging letters from friends—so many of them Coronary Alumni, many cards and gay messages, the pretty, young student nurses, and the frequently repeated ECG's and blood samples.

Very amusing was the amazement of the hospital staff—"Stresses in dermatology?"

It came just after the meeting in Rochester, on Sept. 6, of the Minnesota Dermatological Society on the occasion of the second Paul A. O'Leary Memorial Lecture. The exciting cause might well have been Don Pillsbury's most surprising story of the *faux pas*.

Pillsbury was the Memorial Lecturer—his subject, "Some Thoughts on Syphilis." He emphasized the important role that the disease played in arousing interest on the part of Congress in medical problems—interest that is beginning to affect American medicine profoundly. He recalled that O'Leary had exerted great influence in this significant development. Thus, another contribution by syphilis to the history of medicine.

The meeting opened with a review of the psoralens by Sam Becker Jr.—an attempt "to rescue the psoralens from *Life* and *Time* magazines"—a practical account of psoralens' accomplishments, failures, assets, and faults, and he concluded with a statement to the effect that one cannot decide yet whether psoralen is a good drug or a harmful one, but "certainly it is an interesting one."

Then followed a symposium on the Protean Manifestations of Scleroderma in which members of various departments at Mayos considered visceral aspects, treatment, and classification. Winkelmann, the moderator, introduced each talk in interesting fashion and skillfully guided the discussions which, incidentally, demonstrated clearly that dermatologists have contributed more to the knowledge of this systemic disease than have our medical colleagues.

The clinical demonstrations, as usual, were thrilling to the visitors. Altogether, it was a most appropriate program for the occasion.

My enforced bed rest had its compensations—the opportunity to catch up on noncurricular reading, for example. Thoroughly enjoyable were the much-discussed "Dr. Zhivago," about a doctor, and "The Image-Makers," by a doctor. "Dr. Zhivago," incidentally, at one time during his wanderings suffered from what appeared to be a food-deficiency dermatitis. "The Image-Makers" had everything in good measure—medicine, surgery, politics, economics, sex, and as graphic a picture of a cholera epidemic as you could want to read—altogether an exciting book, if not an important one.

Television, too, helped to pass the time—the World Series and football games, but more important, a gratuitous postgraduate course in therapeutics. Television not only tells what to use for many diverse diseases, such as arthritis and rheumatism, congested sinus areas, dandruff, couch, and sour stomach with acid indigestion, but it also explains diagrammatically just how these products do their work. Then, too, there were the old Dr. Kildare pictures.

Not from television, but from more reliable sources, we learned that Ellis, in Baltimore, has encountered four cases of clothing dermatitis in one month; two from black trousers, one from a brown suit, and the other, a black bra. Has something new been added? And Frumess, in Denver, has observed a little girl with hula-hoop purpura.

And, in New York, there was a woman "who belongs in the collagen diseases."

H. R.

Abstracts from Current Literature

Generalized Micropapular Dermatosis with Reticulofibrocytic Structure, Accompanied by Alterations of the Stroma; New Form of Cutaneous Reticulosis? S. G. Nicolau and L. Balus, Ann. dermat. et syph. 85:146-156 (March-April) 1958.

This case seems to be identical with one described by Thiers and co-workers. Reddish tumefactions appeared in face and neck, the sternoclavicular regions, and the extremities over a period of three years. The adjacent skin became firm and thickened, causing a certain impairment of motion. The elemental lesions are small papules, which, on enlarging, coalesce. Biopsy showed atrophy of the epidermis. Most of the hair follicles were dilated and hyperkeratotic, accompanied by a cystic dilatation of the deeper portions. There was a cellular infiltrate in the dermis composed of numerous young mesenchymal cells. These cells were scattered about without orderly arrangement, in masses of infiltrate. There was no alteration of general health; the authors consider this a new type of benign cutaneous reticulosis.

Derbes, New Orleans.

Cutaneous Hemopoiesis in the Course of Intrauterine Life. L. Popoff and N. Popoff, Ann. dermat. et syph. 85:157-167 (March-April) 1958.

Eighty-six embryos of differing ages demonstrated hemopoietic activity in all skin areas. The earliest hemopoietic differentiation of the mesenchyme begins in embryos of 8 cm. length. Initially, these foci are exclusively erythroblastic. Other blood elements appear later, beginning with the fifth month of fetal development. This function continues in fetuses of 44-50 cm. in the last two months of intrauterine life. These researches permit the explanation of different hemopoietic dermopathies by allowing the autochthonous reactivation of fetal conditions in postnatal life.

Derbes, New Orleans.

Melanoderma in Bright's Disease. H. Thiers, P. P. Ravault, D. Colomb, and E. Lejeune, Ann. dermat. et syph. 85:267-277 (May-June) 1958.

Two examples of melanoderma in the course of chronic renal insufficiency associated with important nitrogen retention are reported. The authors favor the hypothesis of Becher, who attributes the increased pigmentation to accumulation of aromatic nuclei, including phenols, tyrosine, tryptophan, indican, and the like, which are more or less closely related to melanine. Clinically, the pigmentation is a homogeneous grayish or dirty brown. It is influenced by sunlight and is more intense on uncovered parts of the body. Buccal mucosa is exempt, and the genitalia and nipples are not more darkly colored than normal. The pigmentation is independent of the azotemic pruritus.

Derbes, New Orleans.

Miescher's Cheilitis Granulomatosa with Multiple Skin Manifestations Suggesting Lupus Erythematosus. X. Vilanova, J. Pinol Aguadé, and C. Cardenal, Ann. dermat. et syph. 85:278-289 (May-June) 1958.

A case is described of cheilitis granulomatosa evolving over a four-year period in a 14-year-old boy, accompanied by erythematosquamous and atrophic lesions of the back of the hands, the fingers, and the face. In spite of clinical and histologic analogies to lupus erythematosus, the authors believe rather that this represents and extrafacial localization of a general or systemic disease in which cheilitis is usually the major manifestation but which can be accompanied by mono- or oligosymptomatic manifestations.

Derbes, New Orleans.

Frequency of Syphilis in the Musulman Population of Algeria. Francois-Georges Marill and Claude Zerbib, Ann. dermat. et syph. 85:290-296 (May-June) 1958.

The authors analyzed 11,441 observations of patients who were being treated in hospitals between 1950-1955 in two different cities, Algiers and Constantine: patients certainly syphilitic,

733 (6.4%); patients with positive serologic tests without clinical evidence of syphilis, 1,612 (7.6%). The largest number of patients with syphilis had skin manifestations (71.3%), but visceral syphilis was not exceptional, especially of the central nervous system (34 tabes and 26 general paresis out of 667 syphilitic persons).

DERBES, New Orleans.

A PORPHYRIC FAMILY. JULIO M. BORDA and SERGIO G. STRINGA, Arch. argent. dermat. 8:1 (March) 1958.

Three members of one family showed clinical manifestations of cutaneous porphyria. In two, the lesions appeared at the age of four years; one of them presented a typical mutilating porphyria, but the porphyrin could not be demonstrated in abnormal quantities in the urine. The third case presented bullous and erosive lesions, a pemphigoid picture simulating Duhring's disease, a clinical variety not previously described in this disease.

CANIZARES, New York.

TREATMENT OF VITILIGO. DAVID GRINSPAN and RICARDO CALANDRA, Arch. argent. dermat. 8:11 (March) 1958.

The authors present the results obtained in the treatment of vitiligo through the mechanical excitation of the skin by the superficial penetration of needles of a tattooing machine after the application of an oily preparation containing gold. In this article the authors review their experience of five years in 100 patients. Only small localized areas are suited to such treatment, and the best response is obtained on those lesions situated on the face; 54% have yielded satisfactory results. The color of the normal skin of the patient did not seem to influence the results; no Negro patients were treated. The best response was obtained with a machine producing about 3,000 vibrations per minute. In extensive vitiligo having only islands of normal skin, it is better to depigment the latter areas with trichloroacetic acid rather than to stimulate pigmentation in the depigmented areas.

CANIZARES, New York.

MORPHOLOGIC AND HISTOCHEMICAL FINDINGS IN PATHOLOGIC STRATUM CORNEUM, PARTICULARLY IN PARAKERATOSIS: CONTRIBUTION TO BIOLOGY OF SKIN SURFACE. G. K. STEIGLEDER, Arch. klin. u. exper. Dermat. 207:209-229, 1958.

Disturbed keratin formation and disturbed composition of the stratum corneum must be distinguished. Both processes are often combined, since one process influences the other and both are dependent on the epidermis beneath. The horny layer has a characteristic structure according to its location. Pathologic parakeratotic horny layer may variably differ from normal horny layer in morphology and histochemistry. Parakeratotic horny layer shows positive histochemical reactions to certain enzymes, such as acid phosphatase, nonspecific esterases, and β-glucuronidase. The author reviews his own work on the histochemistry of the stratum corneum as well as the pertinent literature.

HOLLANDER, Springfield, Mass.

MECHANISM OF SEROLOGIC SYPHILIS REACTIONS. S. G. NICOLAU, A. BADANOIU, and G. NICOLAU, Arch. klin. u. exper. Dermat. 207:230-243, 1958.

With the use of artificial serologic systems, nonspecific changes of flocculation but not of complement-fixation reactions for syphilis can be produced by increased concentration of total proteins or γ-globulins. Increased concentration of normal lipoids in such systems brings about changes of the complement-fixation reaction only. Increased concentration of lipoids from syphilitic sera causes particularly positive complement-fixation reaction and to a much smaller degree positive flocculation reaction. Combination of syphilis lipoids and γ-globulins produces marked positive flocculation and complement-fixation reactions. These examinations confirm the hypothesis of the lipoproteinic composition of the syphilitic reagin.

HOLLANDER, Springfield, Mass.

CHARACTER OF STERNBERG-REED GIANT CELL IN HODGKIN'S DISEASE. V. APLAS, Arch. klin. u. exper. Dermat. 207:244-250, 1958.

Cytoplasm and nucleus of uni- and multinuclear Sternberg-Reed giant cells contain in great numbers peculiar coccobacilliform micro-organisms which cause severe degenerative changes of the cell structure. The necrobiotic giant cells show distinct basophilic staining.

Sternberg-Reed giant cells are interpreted as parasitic macrophages. The cell parasite is to be identified as the causative organism of Hodgkin's disease.

HOLLANDER, Springfield, Mass.

IMPETIGO HERPETIFORMIS—A SYMPTOM OF CALCIUM DEFICIENCY. G. LEONHARDI and L. MICHEL, Arch. klin. u. exper. Dermat. 207:251-260, 1958.

Impetigo herpetiformis first developed in a 17-year-old youth several months after strumectomy. It subsided after treatment with dihydrotachysterol (A. T. 10). There were two recurrences with symptoms of tetany and hypocalcemia which subsided after therapy with A. T. 10 and vitamin D. Morphologic and histologic findings of subsiding lesions resembled psoriasis. But there is a distinction from psoriasis, since impetigo herpetiformis shows hypocalcemia due to parathyroid deficiency or to calcium deficiency during pregnancy. This calcium deficiency seems to be the cause of impetigo herpetiformis, as it heals promptly under A. T. 10 therapy. Impetigo herpetiformis is an independent disease and is to be separated from the group of psoriasis vulgaris, psoriasis pustulosa, and acrodermatitis continua Hallopeau.

HOLLANDER, Springfield, Mass.

DETERMINATION OF HISTAMINE PEXIS FOR ESTABLISHING ALLERGIC ETIOLOGY. J. TAPPEINER, H. TIRSCHEK, and P. WODNIANSKY, Arch. klin. u. exper. Dermat. 207:261-267, 1958.

Gamma-globulin in the serum of normal persons inactivates in vitro 20%-40% histamine. Parrot and Laborde et al. called this quality of the serum *"pouvoir histaminopéxique,"* "captant," or "histamine pexis." Lack of histamine pexis is supposed to be characteristic of allergic persons. Examination of histamine pexis in 440 patients with various dermatoses showed less than 20% histamine in the majority of dermatoses with allergic etiology, such as eczema, chronic urticaria, and drug dermatitis. A normal captant of 20% and more was found particularly in generalized and localized eczema. Psoriasis always showed histamine pexis of 20% and more, whereas generalized pruritus and erythema multiforme showed values below 20%. Further examinations on a larger number of patients are necessary in order to prove the value of the histamine pexis phenomenon in the allergic etiology of dermatoses.

HOLLANDER, Springfield, Mass.

ANIMAL EXPERIMENTS ON PATHOGENESIS OF ACANTHOSIS NIGRICANS. K. GÄRTNER, Arch. klin. u. exper. Dermat. 207:268-274, 1958.

Removal of the left adrenal, the gonads, or both organs in 14 dogs with acanthosis nigricans and treatment with corticosteroids and adrenal extract in 12 dogs with acanthosis nigricans suggest that acanthosis nigricans of the dog is due to an insufficiency of the mineral corticoid fraction of the adrenals.

HOLLANDER, Springfield, Mass.

HISTOGENESIS OF GIANT-CELL RETICULOHISTIOCYTOMA. F. NÖDL, Arch. klin. u. exper. Dermat. 207:275-290, 1958.

Three isolated nodules of the skin were examined; one was removed because of a possibility of malignant melanoma, and the other two were diagnosed clinically as fibroma. Histologically, two nodules showed in the corium lobular infiltrates of histiocytes and reticular elements with multinucleated giant cells. The third nodule revealed granulomatous structure with uni- and multinuclear giant cells and round cells. The giant cells contained round acidophilic inclusions. The proliferation of reticulohistiocytic elements seemed to come closer in two cases to hyperplasia than true tumor. The importance of primary and secondary foreign toxic substances for the pathogenesis of giant-cell reticulohistiocytoma and related neoplasms is discussed.

HOLLANDER, Springfield, Mass.

MULTIPLE PURE NEURINOMAS OF SKIN. F. NÖDL, Arch. klin. u. exper. Dermat. 207:291-301, 1958.

In a 15½-year-old boy multiple tumors were found on the scalp, trunk, and upper extremities. They commenced to develop at about age 7 years. Most of the somewhat elevated lesions showed hypertrichosis, partly with pili torti, and cutis anserina-like appearance. There were no symptoms of Recklinghausen's disease. The predominantly intraepidermal nodules revealed

histologically a pure neurinoma of polar fibrous Type A (Antoni). The neurinoma cells have grown along preexisting nerves into bundles of smooth muscle.

HOLLANDER, Springfield, Mass.

PRIMARY SCROTAL DAMAGE DUE TO SO-CALLED LYMPHANGIOMA CIRCUMSCRIPTUM CYTOIDES OF THE SCROTUM. R. DOEPFMER and O. HORNSTEIN, Arch. klin. u. exper. Dermat. 207:312-322, 1958.

A 21-year-old man showed lymphangioma circumscriptum cystoides of the scrotum and shaft of the penis. Since age 5 years he suffered repeated attacks of erysipelas of the immensely enlarged scrotum. Histologic examination of specimens of the shaft of the penis and the right testicle, as well as spermatograms, revealed hypospermatogenesis. Fractional short-distance roentgen therapy with protection of the testicles achieved almost complete involution of the lymphangioma and almost normalized the spermatogram. Eight months after roentgen therapy the wife of the patient became pregnant, and a normal male child was delivered in due time. Extramarital conception was considered most improbable. The germinative function of the male gonad is dependent on thermoregulation of a normal scrotum.

HOLLANDER, Springfield, Mass.

DIAGNOSTIC SIGNIFICANCE OF QUANTITATIVE HISTAMINE REACTION IN DERMATOSES. A. W. ENGELHARDT, J. FUNK, and H-J. HEITE, Arch. klin. u. exper. Dermat. 207:339-353, 1958.

In 308 clinic patients (32 with neurodermatitis, 20 with psoriasis, 16 with eczematized psoriasis, 104 with seborrheic dermatitis, 33 with allergic contact dermatitis, and 103 non-eczematous patients with various dermatoses and venereal diseases) the skin reaction to intracutaneous histamine injection was examined by determination of the histamine threshold and by measuring erythema and urtica 15 minutes after injection. There was markedly decreased erythematous and exudative (urticarial) reaction in neurodermatitis. Psoriasis showed normal erythematous and decreased exudative reaction. Allergic contact dermatitis revealed normal erythematous and increased exudative reaction. Histamine reaction as a diagnostic test is of little value in neurodermatitis only.

HOLLANDER, Springfield, Mass.

DIFFERENTIATION OF SYNDROMA MUCOCUTANEOOCULARE ACUTUM FUCHS FROM ERYTHEMA EXUDATIVUM MULTIFORME. H-J. HEITE, M. IHL, and M. WEBER, Arch. klin. u. exper. Dermat. 207:354-376, 1958.

Review of 988 cases published in the world literature as erythema exudativum multiforme or synonyms and Fuchs syndrome or synonyms. Based on statistic evaluation the following classification is recommended: (1) complete Fuchs syndrome (tetra-symptom-complex with skin, oral, conjunctival, and genital lesions), (2) incomplete Fuchs syndrome (oral lesions but lack of one of the other three symptoms), (3) bi-symptom-complex (multiform skin lesions and pseudomembranous stomatitis), (4) erythema multiforme with skin lesions only or additional conjunctival symptoms. Data on frequency of symptom combinations, sex, age, frequency and duration of fever, distribution and kind of skin lesions, and seasonal frequency are presented.

HOLLANDER, Springfield, Mass.

PATHOGENESIS OF ACNE CONGLOBATA. H. FISCHER and I. KÄPPEL, Arch. klin. u. exper. Dermat. 207:377-396, 1958.

Two clinical observations and twenty-two examinations of records from a veterans' hospital and the dermatologic clinic at Tübingen showed a concurrence of acne conglobata and previous brain injury.

HOLLANDER, Springfield, Mass.

HISTOPATHOGENESIS OF SO-CALLED MYOBLASTOMYOMA. F. NÖDL, Arch. klin. u. exper. Dermat. 207:397-412, 1958.

In a 37-year-old woman multiple semiglobular nodules developed within two decades in the jugular fossa on the left forearm and in the pubic and left inguinal regions. In a 14-year-old girl a semiglobular cherry-sized nodule was found on the right forearm. Recklinghausen's disease was also present in this case. With exception of the tumor of the left forearm, a histiocytoma, histologic examination of all nodules revealed myoblastomyoma. Peculiar staining

features of the granular plasma of syncytial tumor cells and their relation to nerve fibers are discussed. The origin of the matrix of the granular syncytial tumor cells is still unknown. It has not been determined whether myoblastomyoma represents a true tumor or an unusual slowly progressing hyperplasia and granular degeneration of yet unknown elements, possibly belonging to nerve tissue.

HOLLANDER, Springfield, Mass.

YEAST DIAGNOSIS IN DERMATOLOGY. H. REITH, Arch. klin. u. exper. Dermat. 207:413-430, 1958.

Results of yeast differentiation as routine procedure in the mycology department of the dermatologic clinic at Hamburg-Eppendorf over a five-year period are given. A total of 15,592 specimens from various diseases were examined; 4,171 yeasts were isolated; 204 perfect and 3,128 imperfect yeasts were identified by the methods of Lodder and Kreger van Rij. Candida albicans was found in 1,111 cases—most frequently in gastric juice, oral cavity, sputum, and feces and less frequently in vulva and vagina. Positive findings in skin scales, nails, pus from abscesses, glandular punctates, and smears from ulcers were much lower. Cryptococcus neoformans was never found.

HOLLANDER, Springfield, Mass.

CHANGES IN THE SEBACEOUS FILM DURING PREGNANCY. R. BRUN and A. RITZ, Dermatologica 116:229, 1958.

During the third trimester of pregnancy there is a distinct diminution in the amount of sebum on the skin of the back as measured by the osmic acid test. This is probably due to the large increase in estrogenic hormones during pregnancy.

MONASH, Miami, Fla.

CLINICAL AND EXPERIMENTAL INVESTIGATION OF THE METABOLISM OF PORPHYRIN. R. SCHUPPLI, Dermatologica 116:289, 1958.

The author has determined the amount of porphyrin excreted in the urine in normal persons and in those with various dermatoses. He found that in normal persons 40% showed an increased porphyrin excretion (over 300μg. %). Only in patients with disturbed liver function, as shown by pathologic liver-function test, was there regularly an increased output of porphyrin. In other internal complications there was no change from the percentages of those with normal and those with increased porphyrin.

In patients without light sensitivity but suffering from psoriasis, urticaria, lupus erythematosus, and erythema exudativum multiforme there was no difference from the percentages in normal cases. Only in porphyria cutanea tarda was there a greatly increased output of porphyrin and uroporphyrin in all cases. Half of the cases of light dermatoses other than porphyria cutanea tarda showed normal porphyrin excretion like the normal controls. The production of massive excretion of porphyrin and coproporphyrin in rabbits by feeding of allylisopropylacetylcarbamide (Sedormid) did not result in an increased sensitivity to light. The conclusion is reached that there is no correlation between the amount of porphyrin in the urine and the sensitivity of the skin to light.

MONASH, Miami, Fla.

FAMILIAL PUSTULAR PSORIASIS WITH THE PICTURE OF IMPETIGO HERPETIFORMIS. W. SOLTERMANN, Dermatologica 116:313, 1958.

Based on the observation of five cases of pustular psoriasis and a survey of the literature, the author concludes that impetigo herpetiformis and pustular psoriasis are morphological variants of psoriasis vulgaris, whereas the question of the relationship of acrodermatitis continua and its differentiation from acrolocalized pustular psoriasis is not yet clear.

MONASH, Miami, Fla.

MELANOSIS CAUSED BY CAMOQUIN. E. YOUNG, Dermatologica 116:389, 1958.

Three cases of lupus erythematosus treated with amodiaquin (Camoquin) showed an intensive grayish-brown discoloration of the skin. The sclerae of all three patients were yellow. One patient had in addition a pigmentation of the anus and vulva. The pigmentation on microscopic examination was shown to be due mostly to melanin with some admixture of another pigment, probably amodiaquin, which, like quinacrine (Atabrine), is yellow in color. The pigmentation disappeared when the drug was discontinued.

MONASH, Miami, Fla.

EXPERIMENTAL ECZEMA. M. GOLAY and R. BRUN, Dermatologica 116:408, 1958.

When 1% of dinitrochlorbenzene solution in acetone is applied daily to the nuchal area of guinea pigs and the nipple area is tested for sensitization after 1-17 days, sensitization, with microscopic evidence of spongiosis and histiocytic infiltration, is found 48 hours after the beginning of sensitizing applications. These microscopic changes antedate macroscopic changes by four to six days.

MONASH, Miami, Fla.

EXPERIMENTS WITH SEBUM TEST IN STUDY OF PATHOGENESIS OF ACNE VULGARIS. R. BRUN and N. GRASSET, Dermatologica 116:416,1958.

Using the osmic acid test for sebum on the back in the paravertebral region a short distance above the shoulder blade, the authors obtained the following results: The sebaceous secretion increases considerably between 8 and 17 years of age in both sexes; it then remains fairly constant in males up to 40 years of age, while it tends to diminish in females. The conclusion is reached that there is some, but not a perfect, parallelism between the amount of sebaceous film and the occurrence of acne. Therefore, other factors besides the amount of sebaceous secretion must be involved.

MONASH, Miami, Fla.

Announcement

Man Sought by F. B. I.

The Federal Bureau of Investigation has requested that dermatologists in the United States be alert for any information concerning Frederick J. Tenuto, who is on the Federal Bureau of Investigation's list of the 10 most wanted fugitives. Tenuto is being sought by the Federal Bureau of Investigation for Unlawful Flight to Avoid Confinement for the Crime of Murder.

Tenuto escaped with William F. "Slick Willie" Sutton and three others from Holmesburg Prison, Philadelphia, on Feb. 10, 1947. All of these persons except Tenuto have been recaptured. Tenuto was serving a sentence of 20 to 40 years at the time for the crimes of armed robbery and murder. Tenuto has previously been involved in two prison breaks.

Tenuto was born on Jan. 20, 1915, at Philadelphia. He is 5 ft. 5 in. in height and was last known to weigh 143 lb.; his hair is black and was full when last known but may be thinning now. His eyes are brown; complexion, very dark; education, six years; he has claimed occupations as a butcher's helper, sheet-metal worker, and laborer. He had an imperfect tattoo "S. J." on his left forearm; said tattoo possibly referred to his underworld nickname "Saint John." He has an imperfect tattoo on his right forearm which may be "Ana," "Anna" or "Ama." Dermatologists might particularly note a small brown flesh mole approximately 1 in. from the right corner of his mouth and on a level with his mouth. He has a 1½ in. scar over the right eye. He also has a large irregular burn scar on his chest.

Dermatologists should particularly note that while in prison he suffered from an allergy condition which was described by the prison doctor as follows:

"He has a psoriatic seborrheic eczema; has allergy background. Diet probably a marked factor in this condition. Also, some external contact probably starting from his work while digging ditches."

On examination by a well-known dermatologist, it was stated that the skin condition of Tenuto would in all probability recur. It was also stated that he was apparently allergic to various types of hairs and fibers, inasmuch as it was necessary to furnish him with a cotton mattress while he was in prison.

Treatment for the skin condition while in prison was set forth as follows:

FREDERICK J. TENUTO

With aliases: Leonard Durham, Leonard Durken, John-Thomas Lestella, Frank Pinto, Durso Thornberry, "St. John," "St. Johnny," "The Angel," and others. Wanted for Unlawful Flight to Avoid Confinement—Murder.

"Intramuscular injections of whole blood, 5 cc. every other day and, externally, phenal, 15 gr., menthol, 2 gr., glycerine, 1 dram, liquor-carbonis-detergen, ½ oz. and aqua qs., 4 oz."

If any doctors should treat someone resembling Tenuto in the future or can recall, by examination of records or otherwise, having treated him in the past, it is requested that information concerning that fact be immediately furnished to the nearest office of the Federal Bureau of Investigation or directly to Director J. Edgar Hoover, F. B. I., U. S. Department of Justice, Washington, D. C. Note that Tenuto has in the past carried firearms and should be considered extremely dangerous. It is also reported that he may have suicidal tendencies. No effort should be made to detain him if he is recognized, but at the earliest possible moment the Federal Bureau of Investigation or local police should be contacted.

Announcements

Earl D. Osborne Fellowship in Dermal Pathology.—The fellowship, sponsored by the American Academy of Dermatology and Syphilology, is to provide annually the opportunity for study and training in dermal pathology to a postgraduate student who has completed satisfactorily at least one year or preferably two years of training in dermatology. The stipend is $4,000 a year, divided into four quarterly payments during the year of the fellowship. The period of training will be spent at the Armed Forces Institute of Pathology, Washington, D. C., the appointment being subject to approval by the director of the Institute. The American Board of Dermatology and Syphilology, Inc., has approved the Institute for one year of training.

It must be emphasized, however, that a student must complete one year of graduate training, either before or after completion of the Osborne Fellowship, in an institution approved by the Board for three years of training. The primary purpose of the Osborne Fellowship is to train dermatologists in dermal pathology. The large amount of material in dermal pathology on hand at the Institute will be available for study, and original research may be pursued under the direction of the chief of the dermal pathology section of the Institute.

Dermatologists in training who are interested in this fellowship may obtain application blanks from Dr. Hamilton Montgomery, Chairman of the Committee on Pathology of the American Academy of Dermatology and Syphilology, 200 1st St., S. W., Rochester, Minn. The next available appointment begins July 1, 1960. Early application is urged, and as a rule applications will not be considered after Sept. 1, 1959, for the July 1, 1960, appointment.

American Board of Dermatology.—At the Annual Meeting of the American Board of Dermatology the following officers were elected:

Dr. Francis W. Lynch—President
Dr. Marcus R. Caro—Vice-President
Dr. Beatrice Maher Kesten—Secretary
Dr. Walter C. Lobitz Jr.—Assistant Secretary
Dr. Louis A. Brunsting
Dr. J. Lamar Callaway
Dr. John M. Lamb
Dr. Clinton W. Lane
Dr. J. Walter Wilson

The following 12 candidates were certified:

Derbes, Vincent J.
Fleming, George
Funt, Tobias Roger
Gass, Herbert Hermann
Hun, Funan
James, Harriet D.
Johnston, J. Harvey
Kirshbaum, Bernard Adrian
Salin, Rolf W.
Statile, Pasquale Anthony
Stone, Bernard
Watkins, Dale Baxter

The following 61 candidates have successfully completed the examinations and will be certified when they have completed the necessary two years of experience in dermatology:

Alexander, Bronson Raye
Ballinger, William George
Barnett, James R.
Beyer, Eugene F.
Brubaker, Marian Merrill
Clearihue, Joyce Golding
Cummiskey, Paul Vernon
Daniels, Farrington, Jr.
Dannenberg, Marvin
Davidson, Wallace N., Jr.
Ewens, George B.
Flanagan, Brian Patrick
Franzblau, Michael Joseph
Frolow, Gerald Ralph
Fusaro, Ramon Michael
Harber, Leonard Coleman
Hassel, Jr., Carl Walter
Hiscock, Roy Burnett, Jr.
Iverson, H. Victoria
Jacobs, Paul H.
James, Kenneth William
Johnson, Waine Cecil
Key, Marcus M.
Krasner, Frank
Lavette, William Michael
Lea, Walker Alfred, Jr.
Leibsohn, Eugene
Lewis, Robert Alexander
Lindsay, Donald Gene
Loria, Philip Ronald

McAndrew, John J.
McCarthy, John Thomas
McFadden, Archibald Weems
Mitchell, Donald Gilbert
Norman, Clyde Wayne
Norris, Edward P., Jr.
Orkin, Milton
Parrott, Norman A.
Pearson, Roger W.
Rosenthal, Albert Lester
Roy, Marcel
Sage, Roderick Duncan
Schoenfeld, Robert John
Schuster, Donald S.
Shapiro, Lewis
Smith, Ernest Wendell
Spiller, Rachel Glynn Ford
Stoll, Howard L., Jr.
Swan, Robert Edward
Tisserand, John B., Jr.
Turra, James L.
Vineyard, William R.
Wagner, William Jordan, Sr.
Watkins, Charles William
Weinmann, Paul L.
Wheeless, John V., Jr.
Williams, Ollie Penn
Windhorst, Dorothy Baker
Johnsen, Rolf Eric
Rapaport, Joseph
Weinreb, Marvin Seymour

The next written examination will be held in major cities on Oct. 5, 1959. The next oral examinations will be held at the University of Oklahoma Hospital, Oklahoma City, from Jan. 15 to 18, 1960. The final date for filing all applications is July 1, 1959.

University of Oklahoma.—A postgraduate course in radiation treatment will be given by the Department of Dermatology of the University of Oklahoma School of Medicine, stressing the use of radium external plaques and interstitial radium element needles, a one-week course April 13-20, 1959. The course will be limited to 30 members or associate members of the American Academy of Dermatology, and 5 third-year residents in dermatology. Demonstration will be made by closed television circuit at the medical school.

The fee is $100 each for Fellows and Associates of the American Board of Dermatology (deductible), payable to the Dermatologic Trust Fund of the University of Oklahoma School of Medicine.

Write to John H. Lamb, M.D., 705 Medical Arts Building, Oklahoma City, for reservations.

Books

Principles of Internal Medicine. Second edition. Edited by T. R. Harrison et al. Price, $21 (2-volume professional edition). Pp. 1,790, with 213 illustrations. The Blakiston Company (division of McGraw-Hill Book Company, Inc.), 330 W. 42d St., New York 36, 1954.

This new edition of the Harrison-edited book, a long-established, authoritative, and thoroughly modern text, contains for the first time a section devoted to "Diseases Affecting the Skin," albeit "limitations of space confined it to a brief discussion of the more pertinent aspects of dermatology." In the twenty pages allotted to this section, Donald Pillsbury skillfully presents the material so that the alert practitioner may quickly identify a lesion as representing either a common or an uncommon disease, banal or serious, a local disturbance or a manifestation of a systemic disease. He mentions representative examples of the various groups and discusses briefly essential clinical characteristics and special procedures, such as the biopsy and the Tsanck test, but he relies most heavily, in ten of the twenty pages, on a presentation of the fundamentals such as applied anatomy, pathology and physiology, morphologic patterns of disease, and history-taking with its related factors of age, race, seasonal incidence of diseases, etc. Discussion of individual diseases is limited to acne, superficial fungus infections, pemphigus, eczema, and exfoliative dermatitis. All of it is, as to be expected, concise and well written in a manner to bear the stamp of an authoritative teacher.

The book contains much more of dermatology, however, than what is contained in the few pages allotted to Pillsbury. All of it, significantly, is written by nondermatologists. The venereal diseases; the erythemas, Bazin's disease, erythema multiforme, and erythema nodosum; the collagen diseases; deep fungus infections, bacterial diseases, drug allergies, and even viral diseases, such as herpes simplex, zoster, molluscum contagiosum, milker's nodules, and warts, are presented. They are presented, not by dermatologists, but by internists, pediatricians, immunologists, geneticists, etc. Is this prophetic?

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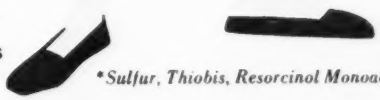

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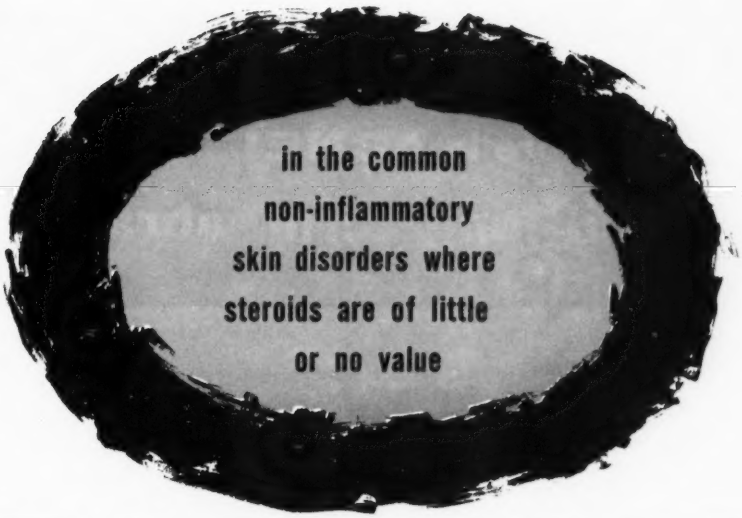

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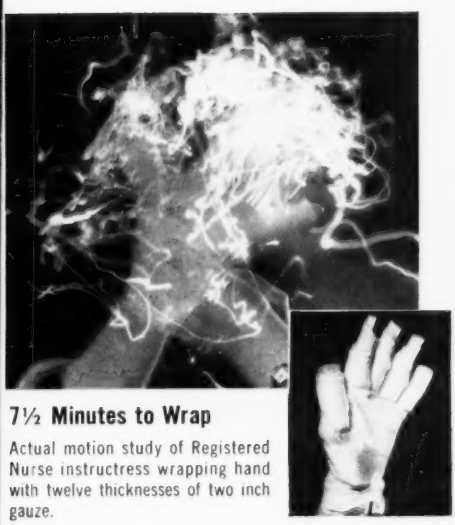
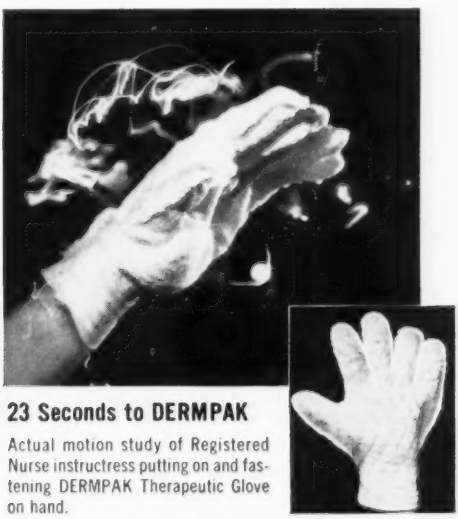


7½ Minutes to Wrap

Actual motion study of Registered Nurse instructress wrapping hand with twelve thicknesses of two inch gauze.



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Actual motion study of Registered Nurse instructress putting on and fastening DERMPAK Therapeutic Glove on hand.

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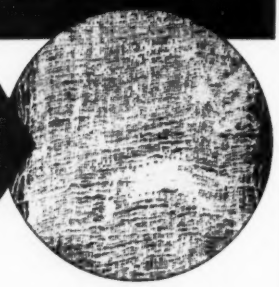

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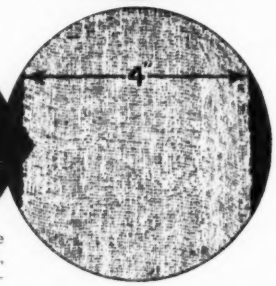

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1. Shaw, J. M., and Crowe, F. W.: Skin Protective Ointments. Arch. Dermat. & Syph. 71: 379, 1955.

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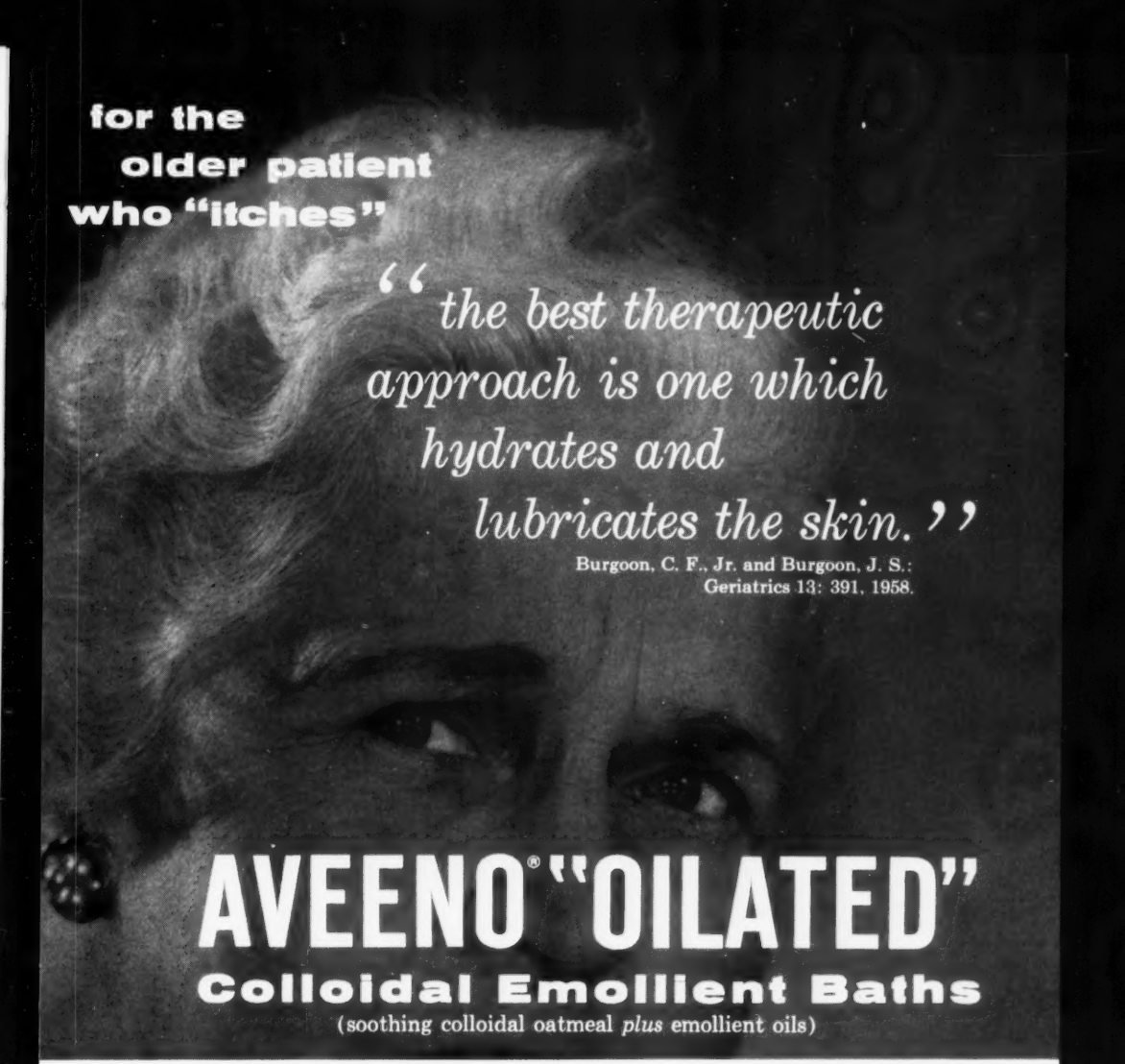
REFERENCE:
Knox, J. M., Everett, M. A., and Curtis, A. C.: New Uses For Surface-Active Agents. A.M.A. Arch. Derm. 74:699-706 (Dec. 1956)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"the best therapeutic approach is one which hydrates and lubricates the skin."
Burgoon, C. F., Jr. and Burgoon, J. S.:
Geriatrics 13: 391, 1958.

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(soothing colloidal oatmeal *plus* emollient oils)

hydrate the skin Tepid colloidal baths supply water of hydration to the dry epithelium.

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References: 1. Sulzberger, M. B. and Wolf, J. Dermatology. Chicago, Year Book Publications, Inc., 1952, p. 42. 2. Grain, M. L.: A.M.A. Arch. Dermat. 58: 402, 1953. 3. Kierland, R. R. and Ede, M.: A.M.A. Arch. Dermat. 63: 602, 1951.

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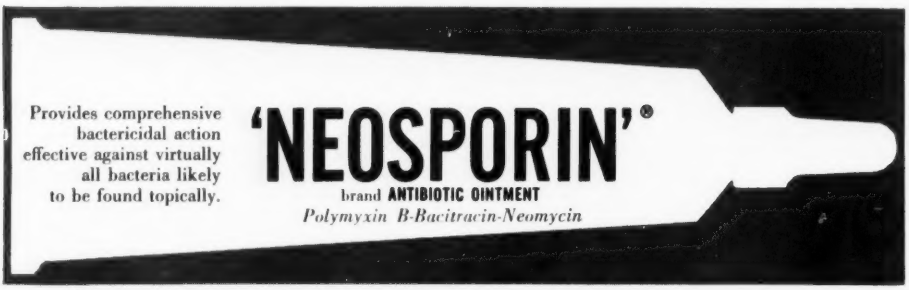
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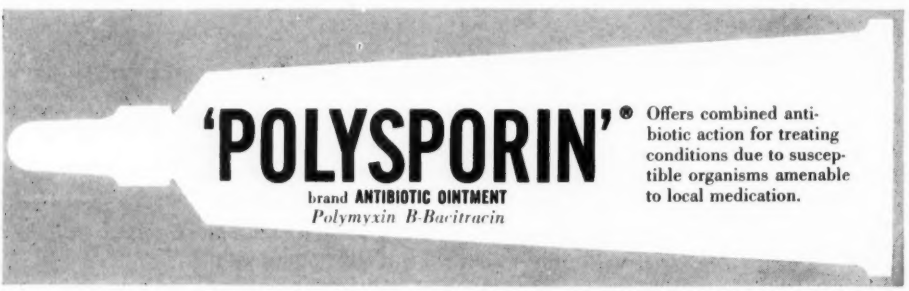
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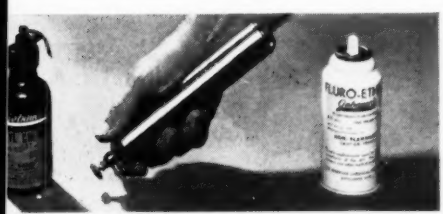

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TELES • is a milk-white, unscented shampoo
TELES • may be employed at weekly intervals or less frequently
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Reference: Gross E. R. and Wright C. S., A. M. A. Archives of Dermatology, 78:92, July, 1958

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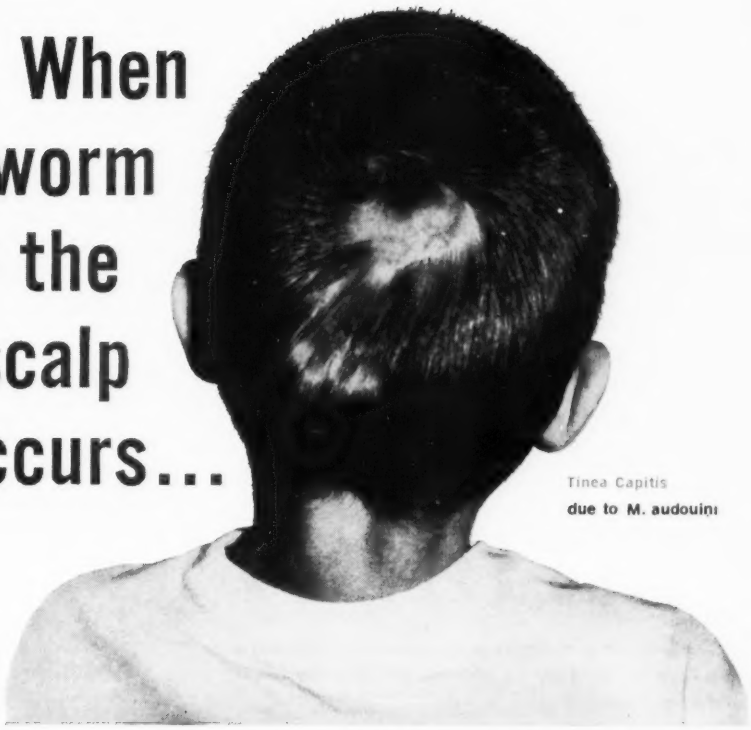

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*New Dosage Form, Salundek Solution** — It is supplied in 3-ounce bottles with a controlled flow applicator cap. Now there is a choice that will lead to better patient cooperation during the treatment of this stubborn disease.

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*In the presence of open lesions, the use of the ointment may be preferred at first since the base of the solution causes occasional transient stinging. Avoid contact with the eyes.

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OINTMENT

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Chlorophyll derivatives—control inflammation, promote the growth of normal, healthy granulations.

PANAFIL Ointment contains papain 10%, urea U.S.P. 10%, and water-soluble chlorophyll derivatives 0.5% in a hydrophilic ointment base. Available in 1-ounce and 4-ounce tubes *on prescription only*.

*Miller, J. M.; Godfrey, G. C.; Ginsberg, M., and Papastrat, C. J., in Surgical Service, V. A. Hospital, Fort Howard, Maryland: Postgrad. Med. *22*:609, 1957.

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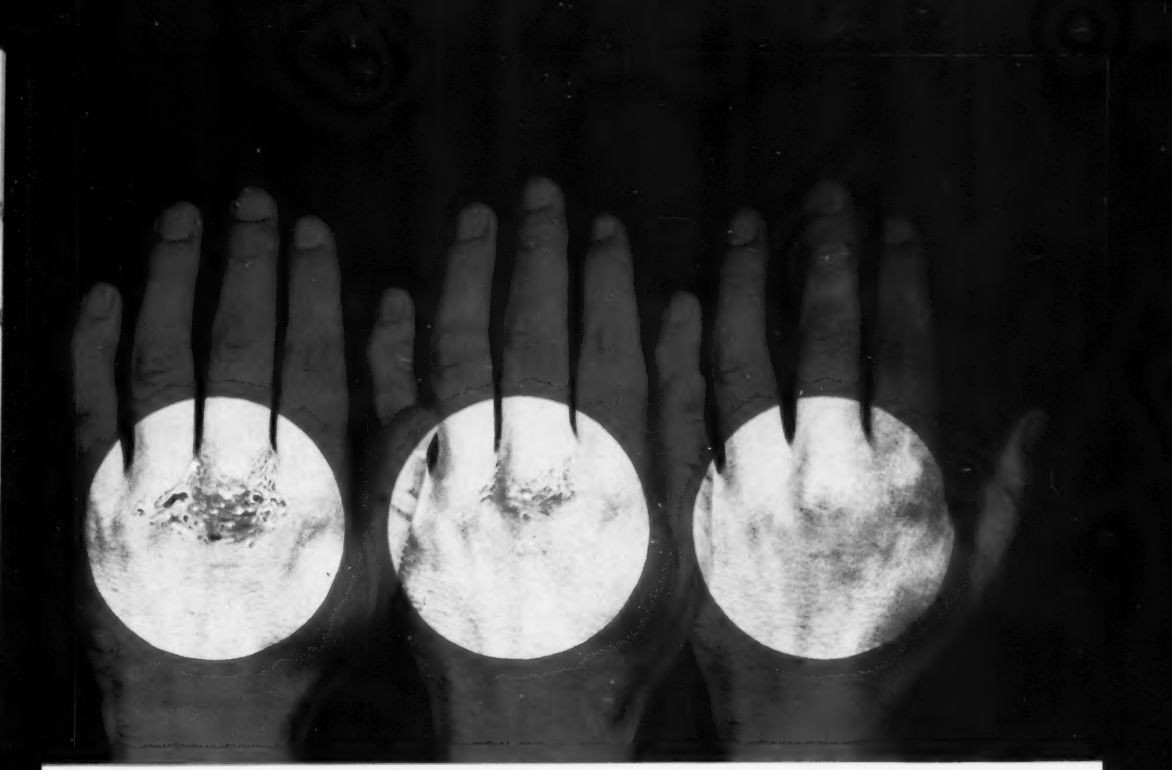

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in the unique Fuzene® base which releases greater antibiotic concentrations than do ordinary grease-base ointments.

NEO-POLYCIN covers the entire range of bacteria most often found in topical lesions... has a low index of sensitivity... averts the risk of sensitization to lifesaving antibiotics, since the antibiotics used in Neo-Polycin are rarely used systemically... is miscible with blood, pus and tissue exudates without loss of efficacy.

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that unidentified allergen may be penicillin

Allergic reactions in patients with no history of penicillin treatment may be caused by penicillin taken in from non-therapeutic sources. Among occult sources of penicillin are:

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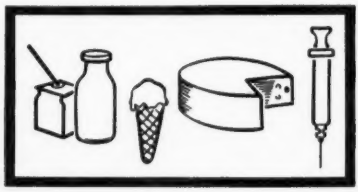
- vaccines including polio vaccine–
- dermatophytes–



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NEUTRAPEN – 800,000 units I.M. – as soon as symptoms appear; may be repeated on the third day if response is not satisfactory. In anaphylactic reactions, epinephrine should be given and other supportive measures instituted immediately, followed by 800,000 units of NEUTRAPEN intravenously and 800,000 units intramuscularly.

contraindications: None.

side effects: Occasionally transient local soreness, erythema, and edema; rarely transitory chills and fever.

supplied: 800,000-unit, single-dose vials of lyophilized penicillinase powder. Stable at room temperature in the dry state.

†Zimmerman, M. C.: Clin. Med. *5*:305, 1958.

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an effective skin moisturizer

moisturizes and softens the skin

promotes moisture retention

supplements natural skin oils

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Lowila Emollient hydrates the skin . . . keeps it soft and smooth

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Lowila Emollient moisturizes the skin and promotes retention of moisture. When applied to the skin, Lowila Emollient provides a partially-occlusive "breathing" film that: (1) supplies its own water to the dehydrated keratin layer, (2) prevents excessive evaporation when the atmosphere is dry, (3) allows the skin to absorb water from an atmosphere with normal humidity.

Lowila Emollient also supplements natural skin oils, restoring the protective action of skin lipids lost through effects of water, weather and detergents. In Lowila Emollient, Kerohydric is dispersed in a lactic acid buffered emulsion that restores and maintains normal skin acidity.

LOWILA EMOLLIENT

Indications

For dryness, flaking and scaling following therapy of acute inflammation
Dermatitis of the hands ("Housewives' eczema")
In chronic atopic dermatitis
Pruritus senilis—pruritus hiemalis
In nummular dermatitis
In psoriasis
Xerosis or asteatosis
Sunburn
Diaper rash
Chafed or chapped skin
Ichthyosis

Caution: Lowila Emollient is partially occlusive. Therefore it should not be used until the skin is free of inflammation.

Application:

Gently rub a small amount into affected areas three or more times a day and at bedtime. Use particularly after exposure to water, soap and detergents.

Availability:

Lowila Emollient is supplied in 62.5 gram tubes.

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88% CURE RATE

in a wide variety of PYODERMAS

BACIMYCIN®

[BACITRACIN-NEOMYCIN] OINTMENT

a first choice for dual antibiotic therapy

In a recent study[1] of 53 patients with various types of pyodermas, the use of BACIMYCIN Ointment ". . . resulted in a cure rate of 88%. . . ." Impetigo, infectious eczematoid dermatitis, atopic eczema, secondary infections superimposed on dermatitis venenata, and folliculitis were among the common skin infections that showed marked improvement with BACIMYCIN therapy.

BACIMYCIN rarely produces sensitization or primary irritation.

Supplied in ½ oz. tubes for prescriptions; in 100 gm. jars for hospital use; in ⅛ oz. tubes for ophthalmic use. Also supplied as BACIMYCIN with Hydrocortisone, ⅛ oz. tube with applicator tip.

Literature and samples on request.

1. Greenhouse, J. M., and Ryle, W. C.: A.M.A. Arch. Dermat. & Syph. 69:366 (March) 1954.

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(1.25% COAL TAR FRACTION WITH HYDROCORTISONE 1%)

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supplied: ½-oz. tube

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for keratolytic action

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